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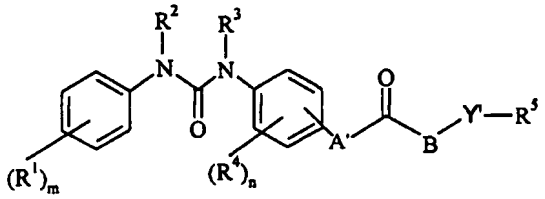

(I)

(57) Abstract

A compound of formula (I) wherein A' is NH or NR^6, where R^6 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkanoyl or C_{1-6}alkoxycarbonyl; B is oxygen or sulphur; Y' is a specified linker group; m is from 0 to 5; n is from 0 to 4; R^1 and R^4 are each independently selected from specified organic groups; and R^5 is an acidic functional group; or a pharmaceutically acceptable salt or *in-vivo* hydrolysable derivative thereof. These compounds are useful in the treatment of a disease or medical condition mediated by the interaction between fibronectin and/or VCAM-1 (especially VCAM-1) and the integrin receptor $\alpha_4\beta_1$.

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DIPHENYLUREA DERIVATIVES

This invention relates to compounds which are inhibitors of the interaction between the integrin $\alpha_4\beta_1$, also known as Very Late Antigen-4 (VLA-4) or CD49d/CD29, and its protein ligands, for example Vascular Cell Adhesion Molecule-1 (VCAM-1) and fibronectin. This invention further relates to processes for preparing such compounds, to pharmaceutical compositions containing them and to their use in methods of therapeutic application.

$\alpha_4\beta_1$ is a member of the integrin family of heterodimeric cell surface receptors that are composed of noncovalently associated glycoprotein subunits (α and β) and are involved in cell adhesion to other cells or to extracellular matrix. There are at least 14 different human integrin α subunits and at least 8 different β subunits and each β subunit can form a heterodimer with one or more α subunits. Integrins can be subdivided based on their β subunit composition. $\alpha_4\beta_1$ is one of several β_1 integrins, also known as Very Late Antigens (VLA).

The interactions between integrins and their protein ligands are fundamental for maintaining cell function, for example by tethering cells at a particular location, facilitating cell migration, or providing survival signals to cells from their environment. Ligands recognised by integrins include extracellular matrix proteins, such as collagen and fibronectin; plasma proteins, such as fibrinogen; and cell surface molecules, such as transmembrane proteins of the immunoglobulin superfamily and cell-bound complement. The specificity of the interaction between integrin and ligand is governed by the α and β subunit composition.

Integrin $\alpha_4\beta_1$ is expressed on numerous hematopoietic cells and established cell lines, including hematopoietic precursors, peripheral and cytotoxic T lymphocytes, B lymphocytes, monocytes, thymocytes and eosinophils [Hemler, M.E. et al (1987), J. Biol. Chem., 262, 11478-11485; Bochner, B.S. et al (1991), J. Exp. Med., 173, 1553-1556]. Unlike other β_1 integrins that bind only to cell-extracellular matrix proteins, $\alpha_4\beta_1$ binds to VCAM-1, an immunoglobulin superfamily member expressed on the cell surface, for example on vascular endothelial cells, and to fibronectin containing the alternatively spliced type III connecting segment (CS-1 fibronectin) [Elices, M.J. et al (1990), Cell, 60, 577-584; Wayner, E.A. et al (1989). J. Cell Biol., 109, 1321-1330].

The activation and extravasation of blood leukocytes plays a major role in the development and progression of inflammatory diseases. Cell adhesion to the vascular

endothelium is required before cells migrate from the blood into inflamed tissue and is mediated by specific interactions between cell adhesion molecules on the surface of vascular endothelial cells and circulating leukocytes [Sharar, S.R. et al (1995). Springer Semin. Immunopathol., 16, 359-378]. $\alpha_4\beta_1$ is believed to have an important role in the recruitment of lymphocytes, monocytes and eosinophils during inflammation. $\alpha_4\beta_1$ /ligand binding has also been implicated in T-cell proliferation, B-cell localisation to germinal centres, haemopoeitic progenitor cell localisation in the bone marrow, placental development, muscle development and tumour cell metastasis.

The affinity of $\alpha_4\beta_1$ for its ligands is normally low but chemokines expressed by inflamed vascular endothelium act via receptors on the leukocyte surface to upregulate $\alpha_4\beta_1$ function [Weber, C. et al (1996), J. Cell Biol., 134, 1063-1073]. VCAM-1 expression is upregulated on endothelial cells *in vitro* by inflammatory cytokines [Osborn. L. et al (1989) Cell, 59, 1203-1211] and in human inflammatory diseases such as rheumatoid arthritis [Morales-Ducret, J. et al (1992). J. Immunol., 149, 1424-1431], multiple sclerosis [Cannella, B. et al., (1995). Ann. Neurol., 37, 424-435], allergic asthma [Fukuda, T. et al (1996), Am. J. Respir. Cell Mol. Biol., 14, 84-94] and atherosclerosis [O'Brien, K.D. et al (1993). J. Clin. Invest., 92, 945-951].

Monoclonal antibodies directed against the α_4 integrin subunit have been shown to be effective in a number of animal models of human inflammatory diseases including multiple sclerosis, rheumatoid arthritis, allergic asthma, contact dermatitis, transplant rejection, insulin-dependent diabetes, inflammatory bowel disease, and glomerulonephritis.

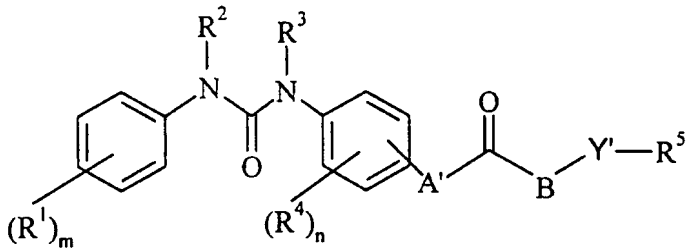
Integrins recognise short peptide motifs in their ligands The minimal $\alpha_4\beta_1$ binding epitope in CS-1 is the tripeptide leucine-aspartic acid-valine (Leu-Asp-Val) [Komoriya, A., et al (1991). J. Biol. Chem., 266, 15075-15079] while VCAM-1 contains the similar sequence isoleucine-aspartic acid-serine [Clements, J.M., et al (1994). J. Cell Sci., 107, 2127-2135]. The 25-amino acid fibronectin fragment, CS-1 peptide, which contains the Leu Asp-Val motif, is a competitive inhibitor of $\alpha_4\beta_1$ binding to VCAM-1 [Makarem, R., et al (1994). J. Biol. Chem., 269, 4005-4011]. Small molecule $\alpha_4\beta_1$ inhibitors based on the Leu-Asp-Val sequence in CS-1 have been described, for example the linear molecule phenylacetic acid-Leu-Asp-Phe-D-Pro-amide [Molossi, S. et al (1995). J. Clin. Invest., 95, 2601-2610] and the disulphide cyclic peptide Cys-Trp-Leu-Asp-Val-Cys [Vanderslice, P., et al (1997). J. Immunol., 158, 1710-1718].

More recently, non- and semi-peptidic compounds which inhibit $\alpha_4\beta_1$/VCAM binding and which can be orally administered have been reported in for example, WO96/22966 and WO98/04247.

There remains a continuing need for alternative compounds which inhibit the interaction between VCAM-1 and fibronectin with integrin $\alpha_4\beta_1$ and, in particular, for compounds which can be administered by an oral route.

We have now found a group of compounds which contain a urethane or carbamosulfanyl linkage which inhibits this interaction.

Accordingly the present invention provides a compound of formula (I)



(I)

wherein

A' is NH or NR^6, where R^6 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkanoyl or C_{1-6}alkoxycarbonyl;

B is oxygen or sulphur;

Y' is a linker group comprising an optionally substituted hydrocarbyl chain which is optionally interposed by one or more heteroatoms independently selected from oxygen, nitrogen and sulphur and/or by a monocyclic or bicyclic ring system; or linker group Y' and A' can be taken together to form a 5 to 7 membered heterocyclic ring, optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

m is from 0 to 5;

n is from 0 to 4;

R^1 and R^4 are each independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6} alkylamino,

di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, N,N-di-[(C_{1-6}alkyl]carbamoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_tOH$ where t is 1 or 2, $-CO_2R^a$ and $CONR^aR^b$ where R^a and R^b are independently hydrogen or C_{1-6} alkyl or one of R^4 can be taken together with A' to form a 5 to 7 membered heterocyclic ring optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-3} alkanoyl or C_{1-6} alkoxycarbonyl; and

R^5 is an acidic functional group;

or a pharmaceutically acceptable salt or in-vivo hydrolysable derivative thereof.

As used herein, the term "hydrocarbyl chain" as used in relation to linker Y' refers to an alkylene, alkenylene and alkynylene group, for example of from 1 to 10 carbon atoms in the case of the alkylene group and from 2 to 10 carbon atoms in the case of alkenylene and alkynylene groups which may be optionally interposed with one or more of the groups listed above.

In particular, the linker group is an alkylene chain which is interposed by a monocyclic ring system and optionally also at least one heteroatom. The ring system is preferably a monocyclic ring system as defined hereinafter.

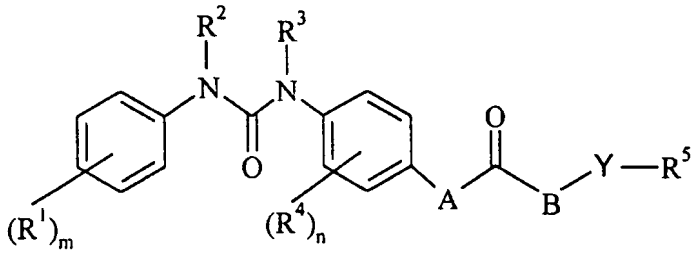
Suitable substitutents for the linker group Y' include any of the groups listed above for R^1 and R^4 as well as aryl groups such as phenyl or naphthyl or aralkyl groups such as benzyl. In particular, the substituents include C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl such as phenyl and aralkyl such as benzyl. Where the linker group Y' includes a nitrogen heteroatom, substitutents may be present on said atom.

Suitably, the linker group is such that the spacing of the group B and the group R^5 by not more than 10 atoms.

In a preferred embodiment, a basic group, and in particular a moiety containing at least one nitrogen is present within linker Y'.

Preferably, the group A' is orientated in the meta or para position with respect to the ureido group in formula (I), and most preferably A' is orientated para- to the ureido group in formula (I).

In a particular embodiment, the invention comprises a compound of formula (IA)



(IA)

wherein

A is nitrogen or NR^6, where R^6 is C_{1-6}alkyl, C_{2-6}alkanoyl or C_{1-6}alkoxycarbonyl;

B is oxygen or sulphur;

Y is a linker group connecting group B to group R^5 and containing up to 10 atoms where each atom is independently selected from carbon, oxygen, nitrogen and sulphur and may optionally comprise a monocyclic or bicyclic ring system or linker group Y and A can be taken together to form a 5 to 7 membered heterocyclic ring, optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

m is from 0 to 5;

n is from 0 to 4;

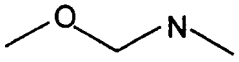
R^1 and R^4 are each independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6} alkylamino, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, N,N-di-[(C_{1-6}alkyl]carbamoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_tOH$ where t is 1 or 2, $-CO_2R^a$ and $CONR^aR^b$ where R^a and R^b are independently hydrogen or C_{1-6} alkyl or one of R^4 can be taken together with A to form a 5 to 7 membered heterocyclic ring optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-3} alkanoyl or C_{1-6} alkoxycarbonyl; and

R^5 is an acidic functional group;

or a pharmaceutically acceptable salt or in-vivo hydrolysable derivative thereof.

It will be understood that Y or Y' preferably excludes those linker groups which are unstable in acid conditions such as those found in the stomach of a human or animal body, for example

 or 

With reference to the compounds of formula (I), the 5 to 7 heterocyclic can be an, optionally substituted, saturated or unsaturated ring with up to three heteroatoms independently selected from nitrogen, oxygen and sulphur. An example of such a ring is an oxazolidinone, oxazolone and thiazolone.

Linker group Y or Y'can comprise a monocyclic ring or a bicyclic ring. With reference to the compounds of formula (I), 'monocyclic ring' means a 5 to 7 membered ring. It can be an, optionally substituted, preferably aromatic ring with up to three heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of such rings include phenyl, pyrimidinyl, pyridyl, imidazolyl, thienyl, thiazolyl, pyridazinyl and pyrrolyl. Other examples include morpholino, tetrahydropyridyl or tetrahydropyrazolyl.

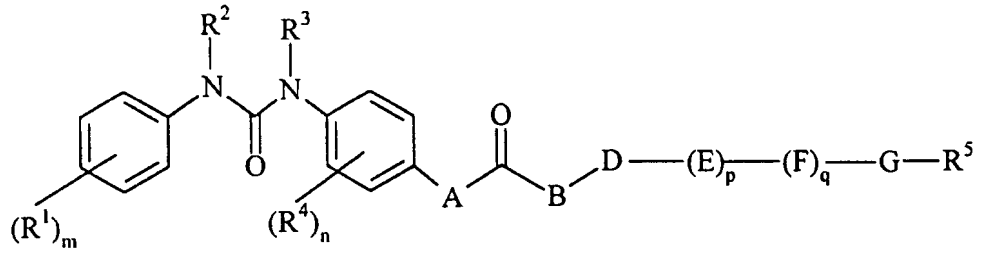
With reference to the compounds of formula (I), 'bicyclic ring system' means an 8 to 10 membered fused ring system wherein one or both rings may contain ring heteroatoms. The ring system may be totally or partially saturated, optionally substituted and contain up to five heteroatoms independently selected from oxygen, nitrogen or sulphur. Examples of suitable ring systems include naphthalene, quinazoline, benzothiophene, benzoxazole, benzothiazole, and benzofuran and the corresponding hydro derivatives, e.g. tetrahydronaphthalene and dihydroquinazoline.

The term 'acidic functional group' means a group which incorporates an acidic hydrogen and includes carboxylic acids, tetrazoles, acyl sulphonamides, sulphonic and sulphinic acids.

In one aspect of the invention, the group Y' or Y is the group

$$- D - (E)_p - (F)_q - G -$$

where D, E, F, G, p and q are as defined below. Thus suitable compounds of the invention are compounds of formula (II)



(II)

wherein

A, B, R^1 to R^5, m and n are as hereinbefore defined;

D and G are each independently C_{1-4} alkyl or C_{2-4} alkenyl and each carbon is optionally substituted with halogeno, hydroxy, amino, nitro, phenyl, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6} alkylamino, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, N,N-di-[(C_{1-6}alkyl]carbamoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_rOH$ where r is 1 or 2, $-CO_2R^7$ and $CONR^7R^8$ where R^7 and R^8 are independently hydrogen or C_{1-6} alkyl, or D and A can be taken together to form a 5 to 7 membered ring, optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

E is phenyl or a monocyclic heterocycle both optionally substituted with up to 3 substituents selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6}alkyl]amino, C_{2-6}alkanoylamino, C_{3-6} alkenoyl- amino, C_{3-6}alkynoylamino, C_{1-6}alkoxycarbonyl, N-C_{1-6}alkylcarbamoyl, N,N-di-[C_{1-6} alkyl]carbamoyl, C_{1-6}alkanoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_sOH$ where s is 1 or 2, $-CO_2R^9$ and $CONR^9R^{10}$ where R^9 and R^{10} are independently hydrogen or C_{1-6} alkyl or E and D can be taken together to form a bicyclic ring system, optionally substituted with up to 3 substituents selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

F is selected from oxygen, sulphur, amino or $CR^{11}R^{12}$;

p and q are each independently 0 or 1;

R^{11} and R^{12} are each independently selected from hydrogen, halogeno, hydroxy, amino, nitro, phenyl, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6} alkylamino, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, N,N-di-[(C_{1-6}alkyl]carbamoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_uOH$ where u is 1 or 2, $-CO_2R^{15}$ and $CNNR^{15}R^{16}$ where R^{15} and R^{16} are independently hydrogen or C_{1-6} alkyl with the proviso that not more than one ring system can be formed from taking together two groups from R^4, A, D and E;

or a pharmaceutically acceptable salt or in-vivo hydrolysable derivative thereof.

With reference to the compounds of formula (II), the 5 to 7 membered ring that can be formed by taking together A and D is a heterocycle ring. It can be an, optionally substituted, saturated or unsaturated ring with up to three heteroatoms independently selected from nitrogen, oxygen and sulphur. An example of such a ring is an oxazolidinone, oxazolone and thiazolone.

With reference to the compounds of formula (II), 'monocyclic heterocycle' means a 5 to 7 membered ring. It can be an, optionally substituted, preferably aromatic ring with up to three heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of such rings include pyrimidinyl, pyridyl, imidazolyl, thienyl, thiazolyl, pyridazinyl and pyrrolyl.

In a further preferred embodiment, the "monocyclic heterocycle" is a non-aromatic heterocyclic ring. Preferably, the rings are linked either to the groups D and/or F by means of a nitrogen atom. Such groups include morpholino, tetrahydropyridyl or tetrahydropyrazolyl.

With reference to the compounds of formula (II), 'bicyclic ring system' means an 8 to 10 membered fused ring system wherein one or both rings may contain ring heteroatoms. The ring system may be totally or partially saturated, optionally substituted and contain up to five heteroatoms, independently selected from oxygen, nitrogen or sulphur. Examples of suitable ring systems include naphthalene, quinazoline, benzothiophene, benzoxazole, benzothiazole, and benzofuran and the corresponding hydro derivatives, e.g. tetrahydronaphthalene and dihydroquinazoline.

The term 'acidic functional group' means a group which incorporates an acidic hydrogen and includes carboxylic acids, tetrazoles, acyl sulphonamides, sulphonic and sulphinic acids.

Particularly preferred values for E in formula (II) is phenyl. Groups D and F are preferably arranged in the ortho- or meta- positions on phenyl ring E, and most preferably are orientated meta- to each other.

Alternatively, E is a monocyclic heterocycle as defined above, and in particular is an N-linked 6 membered non-aromatic heterocycle.

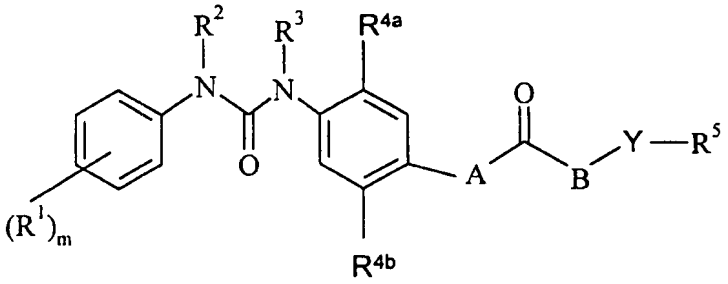
Preferably A' in formula (I) is NH or NR^6 where R^6 is C_{1-6}alkyl such as methyl or C_{2-6}alkenyl such as ethen-2-yl. More preferably A' (or A in Formula (IA) and (II)) is NH or NCH_3 and most preferably A or A' is NH.

Preferably, R^1 is a C_{1-6}alkyl group such as methyl, which is in the ortho position on the phenyl ring relative to the ureido group. Preferably m is 1.

Preferably R^2 and R^3 are hydrogen or C_{1-4} alkyl and most preferably are both hydrogen.

A particular preferred value for B is oxygen.

Particular values for R^4 include C_{1-6}alkyl such as methyl, or C_{1-6} alkoxy such as methoxy. In this case, n is suitably 0, 1 or 2. A particularly preferred group of compounds of formula (I) are those of formula (III)



(III)

where R^1, R^2, R^3, A, B, Y, R^5 and m are as defined above and R^{4a} is either hydrogen or C_{1-6}alkoxy such as methoxy, and R^{4b} is either hydrogen or C_{1-6}alkyl such as methyl.

A preferred value for F in formula (II) is oxygen.

Alternatively, q is 0.

Most preferably R^5 is carboxy.

Suitable values for R^1 to R^4, R^6, R^{11} to R^{16} and for various substituents on Y(or Y'), D, E, F, G or on any ring formed between Yor Y' and A or A', A or A'and D, D and E, A or A' and R^4

include:-

for halogeno:	fluoro, chloro, bromo and iodo
for C_{1-6}alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for C_{2-6}alkenyl:	vinyl, allyl and but-2-enyl;
for C_{1-6}alkanoyl;	formyl, acetyl, propionyl or butyryl;
for C_{2-6}alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for C_{1-6}alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for C_{2-6}alkenyloxy:	vinyloxy and allyloxy;
for C_{2-6}alkynyloxy:	ethynyloxy and 2-propynyloxy;
for C_{1-6}alkylamino:	methylamino, ethylamino, propylamino isopropylamino and butylamino;
for di-C_{1-6}alkylamino:	dimethylamino, diethylamino;
for C_{2-6}alkanoylamino:	acetamido, propionamido and butyramido;
for N-C_{1-6}alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
for N,N-di-C_{1-4}alkylcarbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
for C_{1-6}alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for C_{1-4}alkoxyC_{1-4}alkyl:	methoxymethyl, ethoxymethyl, 1-methoxymethyl, 2-methoxyethyl,

Particularly suitable compounds of formula (II) or pharmaceutically acceptable salts thereof include are those wherein, unless otherwise stated each of R^1 to R^{16}, A, B, D to G, m, p to u has any of the meanings defined hereinbefore or below in sections a to h:-

a) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, E is phenyl, F is oxygen and R^5 is carboxy.

b) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, E is phenyl, F is oxygen and is in the meta position with respect to E and R^5 is carboxy.

c) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, E is phenyl, F is oxygen, R^5 is carboxy and R^1 and R^4 are each independently C_{1-6} alkyl or C_{1-6} alkoxy.

d) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, E is phenyl, F is oxygen, R^5 is carboxy, R^1 and R^4 are each independently C_{1-6} alkyl or C_{1-6} alkoxy and m and n are both 0 or1.

e) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, E is phenyl, F is oxygen, R^5 is carboxy and R^2 and R^3 are each independently C_{1-6} alkyl, preferably methyl.

f) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, E is phenyl, F is oxygen, R^5 is carboxy and R^6 is C_{1-6} alkyl, preferably methyl

g) B is oxygen, D is a C_{1-4} alkyl, optionally substituted as hereinbefore defined, E is phenyl, q is zero and G is a C_{1-4} alkyl or C_{1-4} alkenyl, optionally substituted as hereinbefore defined and R^5 is carboxy.

h) B is oxygen, D and G are each independently C_{1-4} alkyl, optionally substituted as hereinbefore defined, E is phenyl, F is oxygen, A and one of R^4 together form a five membered ring and R^5 is carboxy.

Other particular groups are compounds where

i) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, q is 0, E is morpholino which is N-linked to the group G and is linked to D at the 2 position on the morpholine ring, and R^5 is carboxy.

j) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, q is 0, E is tetrahydropyridyl which is N-linked to the group G and is linked to D at the 4 position on the ring, and R^5 is carboxy;

k) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, q is 0, E is tetrahydropyridyl which is N-linked to the group D and is linked to G at the 4 position on the ring, and R^5 is carboxy;

l) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, q is 0, E is tetrahydropyridyl which is N-linked to the group G and is linked to D at the 2 position on the ring, and R^5 is carboxy;

m) B is oxygen, D and G are each independently a C_{1-4} alkyl, optionally substituted as hereinbefore defined, q is 0, E is tetrahydropyrazinyl which is N-linked to the group D and G, and R^5 is carboxy.

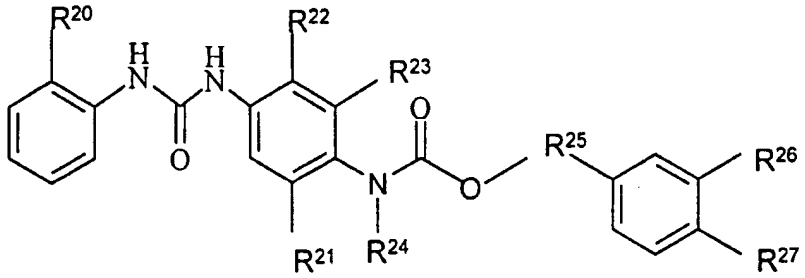
Pharmaceutically acceptable salts include acid addition salts such as salts formed with mineral acids, for example, hydrogen halides such as hydrogen chloride and hydrogen bromide, sulphonic and phosphonic acids; and salts formed with organic acids, especially citric, maleic, acetic, oxalic, tartaric, mandelic, p-toluenesulphonic, methanesulphonic acids and the like. In another aspect, suitable salts are base salts such as alkali metals salts, for example, sodium and potassium; alkaline earth metal salts such as magnesium and calcium; aluminium and ammonium salts; and salts with organic bases such as ethanolamine, methylamine, diethylamine, isopropylamine, trimethylamine and the like. Such salts may be prepared by any suitable method known in the art.

In vivo hydrolysable derivatives include, in particular, pharmaceutically acceptable esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example, intravenously to the test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters for hydroxy include acetyl and for carboxy include, for example, alkyl esters, dialkylaminoalkoxy esters and C_{1-6}alkoxy methyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8} cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl.

It is to be understood that insofar as certain of the compounds of formula (I) as hereinbefore defined may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting the interaction between VCAM-1 and fibronectin with integrin $\alpha_4\beta_1$. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art. These include, for example, synthesis from optically active starting materials or by resolution of a racemic form.

Particular Examples of compound of formula (I) are given in Tables 1, 2 and 3.

Table 1



No.	R^{20}	R^{21}	R^{22}	R^{23}	R^{24}	R^{25}	R^{26}	R^{27}
1	CH_3	H	H	H	H	CH_2	$O(CH_2)_3COOH$	H
2	CH_3	H	OCH_3	H	H	CH_2	$O(CH_2)_3COOH$	H
3	CH_3	H	H	H	H	CH_2	$(CH_2)_2COOH$	H
4	CH_3	H	H	H	H	$CH(CH_3)$	$O(CH_2)_3COOH$	H
5	CH_3	H	H	H	CH_3	CH_2	$O(CH_2)_3COOH$	H
6	CH_3	H	H	H	H	CH_2	$O(CH_2)COOH$	H
7	CH_3	H	H	H	H	$(CH_2)_2$	$O(CH_2)COOH$	H
8	CH_3	H	H	H	H	CH_2	CH=CHCOOH	H
9	CH_3	H	H	CH_3	H	$(CH_2)_2$	$O(CH_2)_3COOH$	H
10	CH_3	H	H	H	CH_3	CH_2	OCH_2COOH	H
11	CH_3	H	H	H	$CH_2CH=CH_2$	CH_2	$O(CH_2)_3COOH$	H
12	CH_3	CH_3	H	H	H	CH_2	OCH_2COOH	H

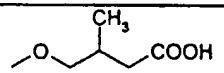
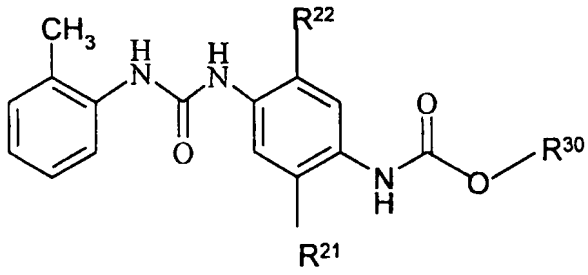
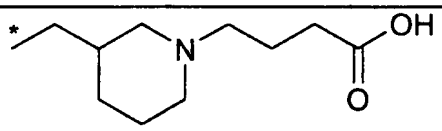
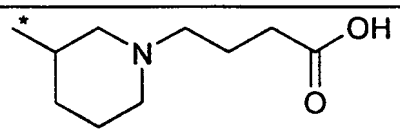
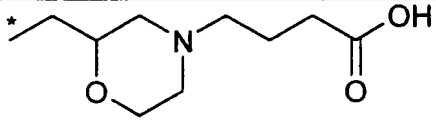
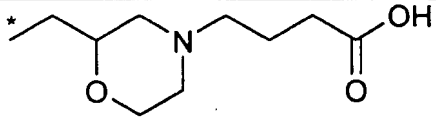
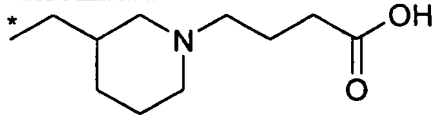
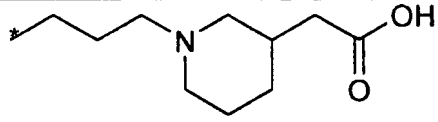
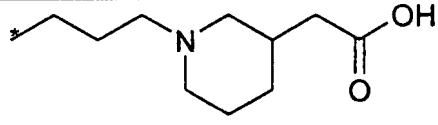
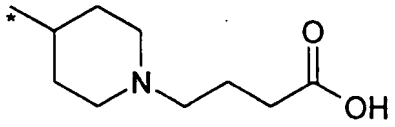
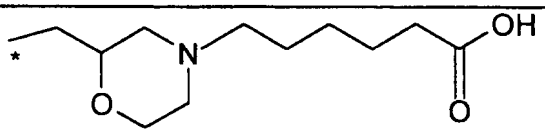
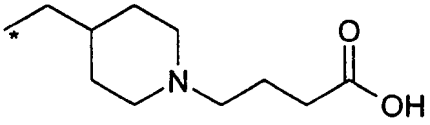
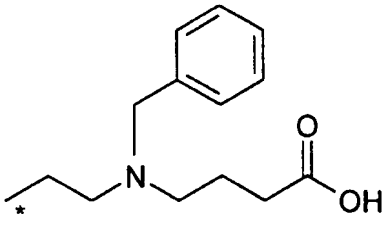
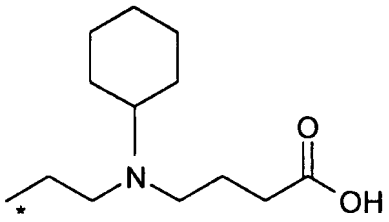
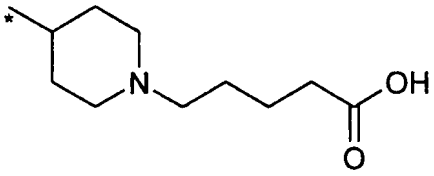
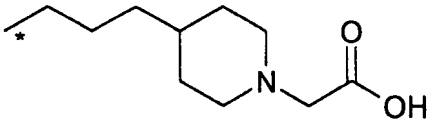
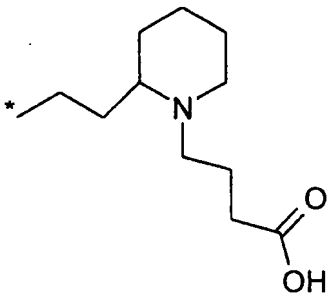
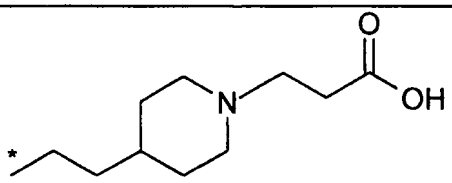
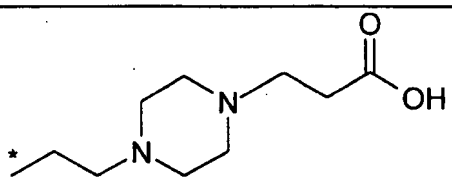
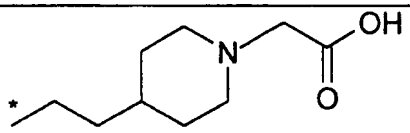
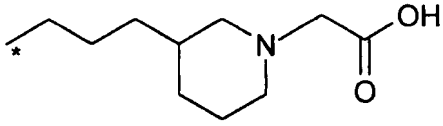
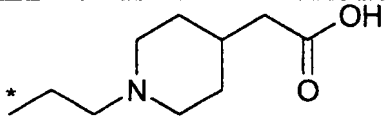
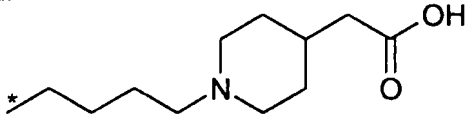
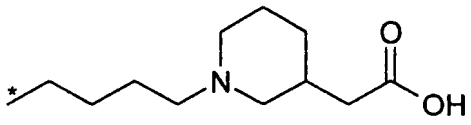
No.	R^{20}	R^{21}	R^{22}	R^{23}	R^{24}	R^{25}	R^{26}	R^{27}
13	CH_3	CH_3	H	H	H	CH_2	$O(CH_2)_3COOH$	H
14	CH_3	H	H	H	H	$CH((CH_2)_2CH_3)$	$O(CH_2)_3COOH$	H
15	CH_3	H	H	H	CH_3	$CH((CH_2)_2CH_3)$	$O(CH_2)_3COOH$	H
16	CH_3	H	H	H	H	CH_2	H	$O(CH_2)_3COOH$
17	CH_3	CH_3	OCH_3	H	H	CH_2	$O(CH_2)_3COOH$	H
18	CH_3	CH_3	OCH_3	H	CH_3	CH_2	OCH_2COOH	H
19	CH_3	H	H	H	H	CH_2	H	OCH_2COOH
20	CH_3	H	H	H	H	CH_2	$O(CH_2)_3COOH$	OCH_3
21	CH_3	CH_3	OCH_3	H	CH_3	CH_2	$O(CH_2)_3COOH$	H
22	CH_3	H	H	H	H	CH_2		H
23	CH_3	CH_3	OCH_3	H	H	CH_2	$CH_2O(CH_2)_2C(O)_2H$	H
24	CH_3	H	H	H	H	CH_2	$CH_2O(CH_2)_2C(O)_2H$	H
25	CH_3	CH_3	OCH_3	H	H	$-CH_2CH_2O-$	OCH_2COOH	H
26	CH_3	CH_3	OCH_3	H	H	$(CH_2)_4$	OCH_2COOH	H
27	CH_3	H	H	H	H	CH_2	COOH	H

Table 2



No	R^{21}	R^{22}	R^{30}
28	H	H	
29	H	H	
30	H	H	
31	CH_3	OCH_3	
32	CH_3	OCH_3	
33	CH_3	OCH_3	
34	H	H	

No	R^{21}	R^{22}	R^{30}
35	CH_3	OCH_3	
36	CH_3	OCH_3	
37	CH_3	OCH_3	
38	CH_3	OCH_3	
39	CH_3	OCH_3	
40	CH_3	OCH_3	
41	CH_3	OCH_3	

No	R^{21}	R^{22}	R^{30}
42	CH_3	OCH_3	
43	CH_3	OCH_3	
44	CH_3	OCH_3	
45	CH_3	OCH_3	
46	CH_3	OCH_3	
47	CH_3	OCH_3	
48	CH_3	OCH_3	
49	CH_3	OCH_3	
50	CH_3	OCH_3	$CH_2CH_2N(CH_3)CH_2CH_2OCH_2CH_2COOH$

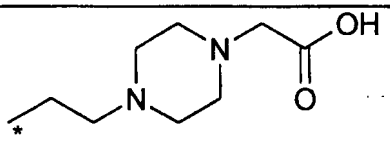
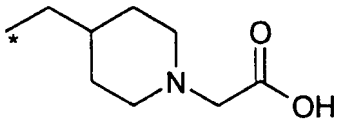
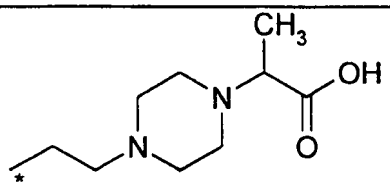
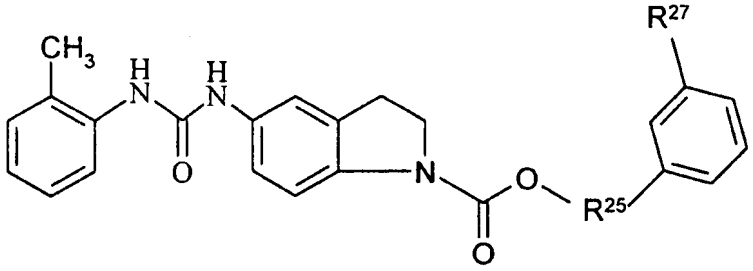
No	R^{21}	R^{22}	R^{30}
51	CH_3	OCH_3	
52	CH_3	OCH_3	
53	CH_3	OCH_3	

Table 3



Compound No	R^{25}	R^{27}
54	CH_2	$O(CH_2)_4COOH$

The activities of the compounds of this invention to inhibit the interaction between VCAM-1 and fibronectin with integrin $\alpha_4\beta_1$ may be determined using a number of in vitro and in vivo screens, as hereinafter defined.

For example, compounds of formula (I) preferably have an IC_{50} of <10μM, more preferably <1μM in the MOLT-4 cell/Fibronectin assay hereinafter described.

In order for it to be used, a compound of formula (I) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof is typically formulated as a pharmaceutical composition in accordance with standard pharmaceutical practice.

Thus, according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof and a pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension, or a depot formulation with drug incorporated in a biodegradable polymer. The composition may be in a form suitable for topical administration such as for example creams, ointments and gels. Skin patches are also contemplated. For these purposes, the compositions of this invention may be formulated by means known in the art, such as for example, as described in general terms, in Chapter 25.2 of Comprehensive Medicinal Chemistry, Volume 5, Editor Hansch et al, Pergamon Press 1990.

Furthermore, the pharmaceutical composition of the present invention may contain one or more additional pharmacological agents suitable for treating one or more disease conditions referred to hereinabove in addition to the compounds of the present invention. In a further aspect, the additional pharmacological agent or agents may be co-administered, either simultaneously or sequentially, with the pharmaceutical compositions of the invention.

The composition of the invention will normally be administered to humans such that the daily dose will be 0.01 to 75mg/kg body weight and preferably 0.1 to 15mg/kg body weight. A preferred composition of the invention is one suitable for oral administration in unit dosage form for example a tablet or capsule which contains from 1 to 1000mg and preferably 10 to 500mg of a compound according to the present invention in each unit dose.

Thus, according to yet another aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect of the invention the present invention provides a method of treating a disease mediated by the interaction between VCAM-1 and/or fibronectin and the integrin receptor $\alpha_4\beta_1$ in need of such treatment which comprises administering to said warm-blooded mammals an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof.

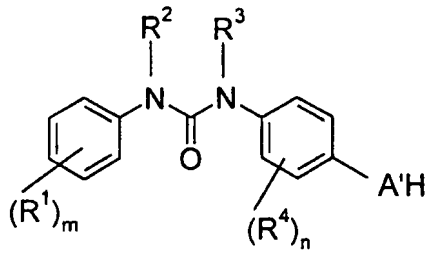
The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof in the production of a medicament for use in the treatment of a disease or medical condition mediated by the interaction between fibronectin and/or VCAM-1 (especially VCAM-1) and the integrin receptor $\alpha_4\beta_1$.

In a preferred embodiment the mammal in need of treatment is suffering from multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease, psoriasis, atherosclerosis, transplant rejection, inflammatory bowel disease, insulin-dependent diabetes and glomerulonephritis.

Preferred compounds of formula (I) for use in these various embodiments of the invention are as set out above and include compounds of formula (IA) or (II).

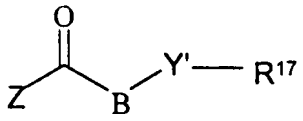
In another aspect of the invention, there is provided a process for preparing a compound of formula (I), a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof which method comprises either

(a) reacting a compound of formula (IV)



(IV)

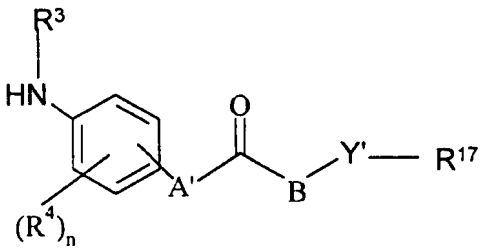
where A', R^1, R^2, R^3, R^4, m and n are as defined in relation to formula (I), with a compound of formula (V)



(V)

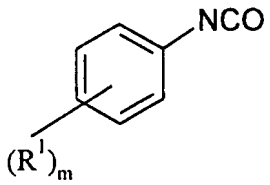
where B and Y' are as defined in relation to formula (I), Z is a leaving group, such as halo, and R^{17} is a group R^5 as defined in relation to formula (I) or a protected form thereof: or

(b) reacting a compound of formula (VI)



(VI)

where A', B, Y' R^3, R^4 and n are as defined in relation to formula (I) and R^{17} is as defined in relation to formula (V) with a compound of formula (VII)



(VII)

where R^1 and m are as defined in relation to formula (I);

and thereafter if desired or necessary,

i) removing any protecting groups; and

ii) optionally forming a pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable derivative.

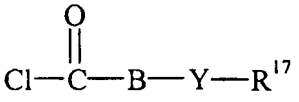
Particular protected groups R^{17} are ester groups an in particular C_{1-6}alkyl esters.

Starting materials for the process may be obtained by standard organic chemistry procedures. The preparation of such starting materials is described in the following representative processes in conjunction with the accompanying Examples. Alternative starting materials are obtaintable by procedures which are analogous to those desctibed below and within the ordinary skill of an organic chemist.

One process (a) above, comprises coupling together a compound of formula (IV) and (V) above, via the formation of a urethane or a carbamosulfanyl. The compounds are suitably reacted together in the presence of an inert solvent and in basic conditions.

A suitable solvent system for the aforementioned process is dichloromethane or tetrahydrofuran (THF) in the presence of pyridine.

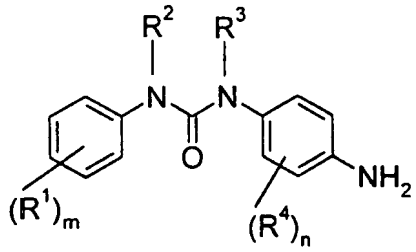
A particular compound of formula (V) is a compound of formula (VIII)



(VIII)

where Y is the group - D - $(E)_p$ - $(F)_q$ - G -

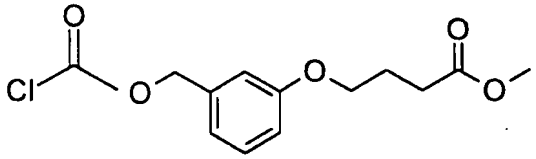
and where B, D, E, F, G, p and q are as hereinbefore defined and R^{17} is a $COOC_{1-6}$ alkyl. A particular example of a compound of formula (IV) is a compound of formula (IX)



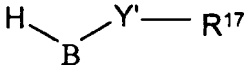
(IX)

where R^1, R^2, R^3, R^4, n and m are as defined in relation to formula (I).

An example of a compound of formula (VIII) where B is oxygen, D is CH_2, E is phenyl, p is 1, q is 1, F is oxygen, G is C_3 alkyl and R^{17} is COOMe



Compounds of formula (V) can be prepared by reacting a compound of formula (X)

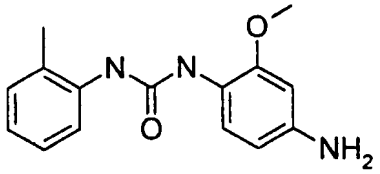


(X)

with phosgene in the presence of toluene/dichloromethane. Where B is oxygen, this compound is the corresponding alcohol.

These alcohols can be prepared by reaching 3-hydroxybenzyl alcohol and methyl 4-bromobutyrate under basic conditions. It will be appreciated that different alcohols can be prepared by substituting, for example, methyl 4-bromobutyrate by t-butylbromoacetate.

An example of a compound of formula (IX) where m and n are both 1, R^1 is methyl, R^2 and R^3 are both hydrogen and R^4 is methoxy is



Such a compound can be prepared from the corresponding 3-methoxy-4(N'-(2-methylphenyl)urea)nitrobenzene. The latter can be prepared from the reaction of the corresponding methoxy-nitroaniline together with methylphenylisocyanate.

It will appreciated by the skilled person that in some of the reactions it may be necessary to protect sensitive groups in the molecule. Protecting groups may typically be chosen from any of the groups described in literature or known to the skilled person.

Suitable protecting groups for an amino group include for example, formyl, and alkoxycarbonyl groups, for example tert-butoxycarbonyl.

Suitable protecting groups for a hydroxy group include lower alkyl groups, for example tert-butyl, and acyl groups, for example an alkanoyl group such as acetyl.

Suitable protecting groups for a carboxy group include, an esterifying group, for example a methyl or ethyl group.

These groups may be removed by any convenient method described in the literature or known to the skilled person for removal of the specific protection group in question. The method of removal is chosen so as to minimise disturbance on the other groups in the molecule. For example when the protecting group is an acyl group or a C_{1-2} alkyl group it may be removed by hydrolysis with a suitable base such as, for example, sodium hydroxide. A tert-butyl protecting group may be removed with, for example, an organic acid such as trifluoroacetic acid .

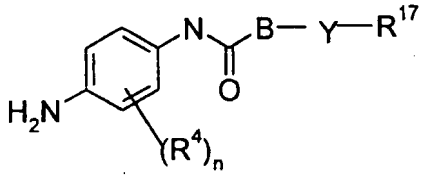
An alternative method of preparing a compound of formula (I), a pharmaceutically acceptable salt or an in vivo hydrolysable derivative comprises reacting together a compound of formula (VI) and (VII), to form a urea linkage. The reaction is suitably effected in the

presence of an inert solvent. Suitable inerts solvents for the aforementioned process include dichloromethane, THF or ethyl acetate. As before, any functional group is protected if necessary and

i) removing any protecting groups; and

ii) optionally forming a pharmaceutically acceptable salt or in vivo hydrolysable derivative.

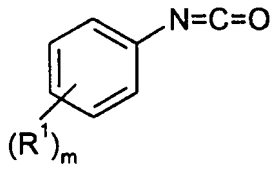
A particular example of a compound of formula (VI) is a compound of formula (XI)



(XI)

where Y is the group - D - $(E)_p$ - $(F)_q$ - G -

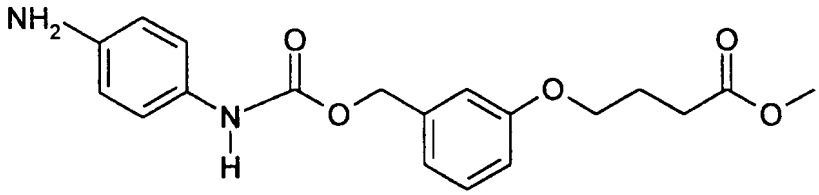
where R^4, R^{17}, B, D, E, F, G, n, p and q are as hereinbefore defined. A particular example of a compound of formula (VII) is a compound of formula (XII)



(XII)

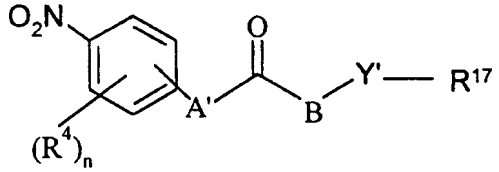
where R^1 and m are as hereinbefore defined.

An example of a compound of formula (V) is



(XIII)

Such a compound can be prepared by reducing the corresponding nitroaniline derivatives. Thus compounds of formula (VI) can be prepared by reduction of a compound of fomula (XVI)

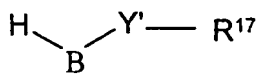


(XVI)

where A', Y', B, R^{17}, R^4 and n are as defined above.

A suitable reduction regime would be iron powder in the presence of ammonium chloride/water/methanol.

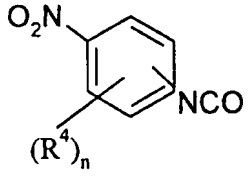
The nitroaniline derivative of formula (XVI) where A' is NH, can be prepared by reacting an appropriate compound of formula (XIV)



(XIV)

where B, Y' and R^{17} are as defined above, and B in particular is oxygen,

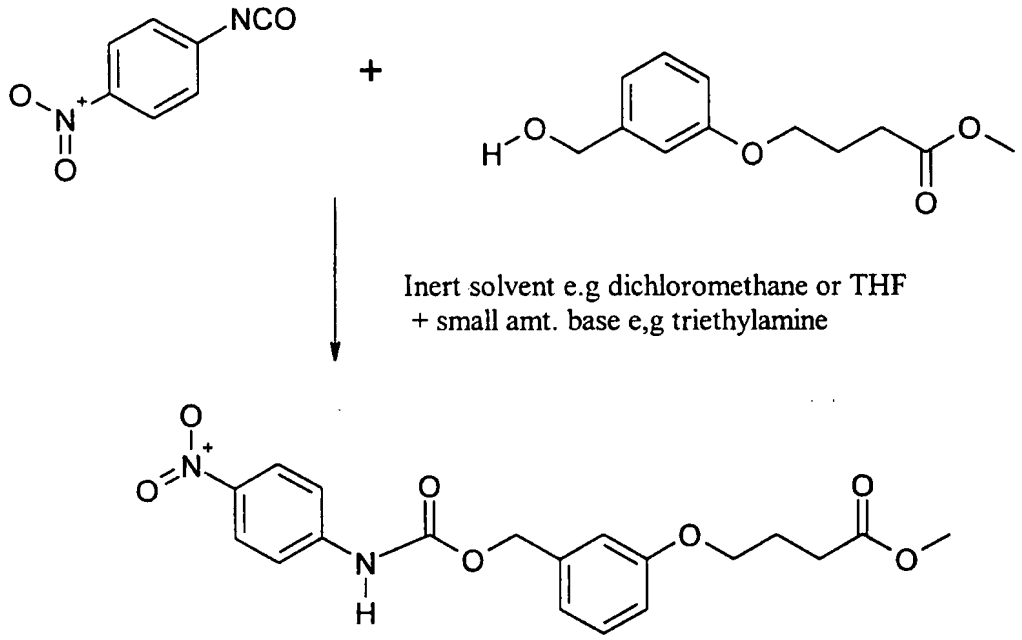
with an isocyanate of formula (XV)



(XV)

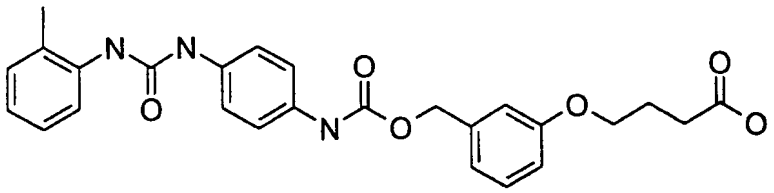
The reaction is suitably effected in an organic solvent such as dichloromethane of tetrahydrofuran (THF) in the present of a base such as triethylamine.

Thus an exemplary scheme is as follows :



The invention is further limited by the following biological test methods, data and non-limiting examples.

Example 1 - Preparation of 4-(3-{[({4-[(2-toluidinocarbonyl)amino]anilino}carbonyl)oxy]methyl}phenoxy)butanoic acid (Compound No. 1 in Table 1)



To methyl-4-(3-{[({4-[(2-toluidinocarbonyl)amino]anilino}carbonyl)oxy]methyl} phenoxy)butanoate (0.085g) in dimethyl sulphoxide (DMSO) (1ml) was added 2N aqueous sodium hydroxide (0.2ml). The mixture was stirred for 1hr at ambient temperature and then water (5ml) added. The pH was adjusted to pH 2 with concentrated hydrochloric acid. The precipitated solid product was filtered and washed with water and then dried to give the acid (0.055g) as a dark brown solid. (68%)

Mass spectrum M-H 476.8

1H nmr (DMSO-d6) : 1.9 (m) 2H; 2.2 (s), 3H; 2.4 (t), 2H; 4.0 (t), 2H; 5.1 (s) 2H; 6.9 (m), 4H: 7.1 (m), 2H; 7.3 (t), 1H; 7.4 (s), 4H; 7.8 (m), 2H; 8.9 (s), 1H; 9.6 (s), 1H.

a) Preparation of methyl 4-(3-hydroxymethyl)phenoxybutyrate

To a mixture of potassium carbonate (5.6g), 3-hydroxybenzyl alcohol (2.5g) in N-methylpyrollidinone (5ml) and methyl 4-bromobutyrate (2.2ml) were added followed by potassium iodide (2g). The mixture was stirred at room temperature for 48 hrs., added to water (30ml) and then extracted with diethyl ether (100ml). The organic layer was washed with dilute sodium hydroxide solution and brine. It was then dried over magnesium sulphate and evaporated to dryness. The residue was then purified by chromatography on silica using an increasingly polar mixture of ethyl acetate/ hexane (20% changing to 90%) to give methyl 4-(3-hydroxymethyl)phenoxybutyrate. (3.1g).

1H nmr ($CDCl_3$) included the following resonances :

2.1 (m), 2H: 2.5 (t), 2H; 3.7 (s), 3H; 4.0 (t), 2H; 4.6 (s), 2H; 6.8 (q), 1H; 6.9 (m), 2H; 7.2 (m), 1H.

b) Preparation of methyl-4-(3-{[({4-[(2-toluidinocarbonyl)amino] anilino}carbonyl)oxy]methyl}phenoxy)butanoate

To methyl 4-(3-hydroxymethyl)phenoxybutyrate (0.22g) in dichloromethane (3ml) was added 20% phosgene in toluene (3ml) and the mixture allowed to stand for 18hrs, evaporated and part of the residue (0.15g) in dichloromethane (2ml) added to 4-(2-tolylureido)aniline (CAS Registry Number 202874-38-2 and as described in WO 98/04247) (0.12g) in dichloromethane (3ml) containing pyridine (0.1g). The mixture was stirred for 2hrs and then evaporated and the residue purified by chromatography on silica using an increasingly polar mixture of methanol/ chloroform (0% changing to 10%) to give, after evaporation and trituration in diethyl ether the above material (0.15g)

Mass spectrum: M+H 492

1H nmr (DMSO-d6) included the following resonances :

2.0 (m), 2H; 2.2 (s), 3H; 2.5 (m), 2H; 3.6 (s), 3H; 4.0 (t), 2H; 5.1 (s), 2H; 6.9 (m), 4H; 7.1 (m), 2H; 7.3 (t), 1H; 7.4 (s), 4H; 7.8 (m), 2H; 8.9 (s), 1H; 9.6 (s), 1H.

Example 2 - Preparation of 4-(3-{[({methyl-4-[(2-toluidinocarbonyl)amino]anilino} carbonyl)oxy]methyl}phenoxy)butanoic acid (Compound No 5 in Table 1)

This was prepared by hydrolysis of methyl-4-(3-{[({methyl-4-[(2-toluidinocarbonyl)amino]anilino} carbonyl)oxy]methyl}phenoxy)butanoate using the process described in example 1

Mass spectrum M+H 492

1H nmr (DMSO-d6) included the following resonances :

1.9 (m), 2H; 2.2 (s), 3H; 2.4 (t), 2H; 3.2 (s), 3H; 4.0 (t), 2H; 5.1 (s), 2H; 6.8 (m), 3H; 6.9 (t), 1H; 7.2 (m), 6H; 7.4 (d), 2H; 7.8 (d), 2H; 7.9 (s), 1H; 9.0 (s), 1H.

a) Preparation of methyl 4-[3-({[(4-nitroanilino)carbonyl]oxy} methyl)phenoxy]butanoate

To methyl 4-(3-hydroxymethyl)phenoxybutyrate (2.24g) in dichloromethane (10ml) was added 4-nitrophenylisocyanate (2g) and triethylamine (3 drops). The mixture was stirred for 2 hrs., evaporated to dryness and the residue triturated with diethyl ether to give methyl 4-[3-({[(4-nitroanilino)carbonyl]oxy}methyl)phenoxy]butanoate as a yellow powder (3.5g)

1H nmr ($CDCl_3$) included the following resonances :

2.1 (m), 2H; 2.5 (t), 2H; 3.7 (s), 3H; 4.0 (t), 2H; 5.2 (s), 2H; 6.9 (m), 3H; 7.1 (s), 1H; 7.3 (d), 1H; 7.6 (d), 2H; 8.2 (d), 2H.

b) Preparation of methyl 4-[3-({[(methyl-4-nitroanilino)carbonyl]oxy} methyl)phenoxy]butanoate

To methyl 4-[3-({[(4-nitroanilino)carbonyl]oxy}methyl)phenoxy]butanoate(1g) in N-methylpyrollidinone (5ml) added sodium hydride (1.1 equ.) and methyl iodide (1.3 equ.) and the mixture stirred for 4hrs, added to water (20ml) and extracted with diethyl ether (50ml), this washed with brine, dried and evaporated to dryness. The residue was purified by chromatography on silica using an increasingly polar mixture of ethyl acetate/ hexane (10% changing to 30%) to give product as a gum (0.8)g which crystallised on standing.

1H nmr ($CDCl_3$) included the following resonances :

2.1 (m), 2H; 2.5 (t), 2H; 3.4 (s), 3H; 3.7 (s), 3H; 4.0 (t), 2H; 5.2 (s), 2H; 6.9 (m), 3H; 7.3 (m), 1H; 7.6 (d), 2H; 8.2 (d), 2H.

c) Preparation of methyl-4-(3-{[({methyl-4-[(2-toluidinocarbonyl)amino] anilino}carbonyl)oxy]methyl}phenoxy)butanoate

To methyl 4-[3-({[(methyl-4-nitroanilino)carbonyl]oxy}methyl)phenoxy] butanoate(0.7g) in methanol (10ml) was added iron powder (0.7g) and a solution of ammonium chloride (0.13g) in water (4ml). The mixture was refluxed for 1hr., ethyl acetate (30ml) added and the mixture filtered to remove metal salts, and evaporated to dryness. The residue in dichloromethane was dried with magnesium sulphate, filtered and evaporated to dryness. The residue in dichloromethane (5ml) was treated with o-tolylisocyanate (1.1 equ.) and allowed to stand for 18hrs., evaporated to dryness and triturated with diethyl ether to give methyl-4-(3-{[({methyl-4-[(2-toluidinocarbonyl)amino] anilino} carbonyl)oxy]methyl}phenoxy]butanoate (0.6g) as an off-white solid.

1H nmr (DMSO-d6) included the following resonances :

2.0 (m), 2H; 2.2 (s), 3H; 2.45 (m), 2H; 3.2 (s), 3H; 3.6 (s), 3H; 3.9 (t), 2H; 5.0 (s), 2H; 6.8 (m), 3H; 6.9 (m), 1H; 7.2 (m), 5H; 7.4 (d), 2H; 7.8 (d), 1H; 7.9 (s), 1H; 9.0 (s), 1H.

Example 3 - Preparation of 4-(3-{[({4-[(2-toluidinocarbonyl)amino]anilino}carbonyl)oxy]methyl}phenoxy)ethanoic acid (Compound No. 6 in Table 1)

Tertiary-butyl-4-(3-{[({4-[(2-toluidinocarbonyl)amino]anilino}carbonyl)oxy]methyl}phenoxy)ethanoate (0.6g) was stirred in a mixture of dichloromethane (4ml) and trifluoroacetic acid (4ml) for 2hrs. and then evaporated to dryness. The residue was triturated in diethyl ether to give 4-(3-{[({4-[(2-toluidinocarbonyl)amino]anilino}carbonyl)oxy]methyl}phenoxy)ethanoic acid as a white powder (0.48g, 87%)

Mass spectrum M-H 448

1H nmr (DMSO-d6) included the following resonances :

2.2 (s), 3H; 4.6 (s), 2H; 5.1 (s), 2H; 6.9 (m), 4H; 7.1 (m), 2H; 7.3 (t), 1H; 7.35 (s), 4H; 7.8 (m), 2H; 8.9 (s), 1H; 9.6 (s), 1H.

a) Preparation of t-butyl 4-(3-hydroxymethyl)phenoxyacetate

To 3-hydroxybenzyl alcohol (95g) in acetone (10ml) was added potassium carbonate (11g) and 1 spoonful of potassium iodide and the mixture stirred whilst t-butylbromo acetate (6.5ml) was added. The mixture was then stirred for a further 18 hrs. The acetone was then evaporated and the residue partitioned between water (60ml) and ethyl acetate (60ml). The organic layer was dried and evaporated and the residue purified by chromatography on silica using an increasingly polar mixture of ethyl acetate in hexane. The appropriate fractions evaporated to dryness gave 7g of white crystalline product.

1H nmr ($CDCl_3$) contained the following resonances :

1.5 (s), 9H; 4.5 (s), 2H; 4.65 (d), 2H; 6.8 (q), 1H; 7.0 (m), 2H; 7.3 (t), 1H.

b) Preparation of t-butyl-4-[3-({[(4-nitroanilino)carbonyl]oxy}methyl)phenoxy]ethanoate

To t-butyl 4-(3-hydroxymethyl)phenoxyacetate (1.2g) in dichloromethane (10ml) was added 4-nitrophenylisocyanate (1.1 equ.) and triethylamine (3 drops). The mixture was stirred for 2 hrs., evaporated to dryness and the residue triturated with diethyl ether to give t-butyl-4-[3-({[(4-nitroanilino)carbonyl]oxy}methyl)phenoxy]ethanoate as a yellow powder (1.7g)

1H nmr (DMSO-d6) included the following resonances :

1.4 (s), 9H; 4.6 (s), 2H; 5.15 (s), 2H; 6.85 (q), 1H; 6.95 (s), 1H; 7.0 (d), 1H; 7.3 (t), 1H; 7.7 (d), 2H; 8.2 (d), 2H.

c) Preparation of t-butyl-4-(3-{[{(4-[(2-toluidinocarbonyl)amino] anilino}carbonyl)oxy]phenoxy)ethanoate

T-butyl-4-[3-({[(4-nitroanilino)carbonyl]oxy}methyl)phenoxy]ethanoate(0.7g) was reduced and reacted with o-tolylisocyanate by the method described in example 2 to give t-butyl-4-(3-{[({4-[(2-toluidinocarbonyl)amino]anilino}carbonyl)oxy]methyl} phenoxy)ethanoate (0.8g) as an off-white powder.

1H nmr (DMSO-d6) included the following resonances :

1.4 (s), 9H; 2.2 (s), 3H; 4.6 (s), 2H; 5.1 (s), 2H; 6.9 (m), 4H; 7.1 (m), 2H; 7.3 (t), 1H; 7.4 (s), 4H; 7.8 (m), 2H; 8.85 (s), 1H; 9.6 (s), 1H.

Example 4 - Preparation of 4-(3-{[({3-methoxy-4-[(2-toluidinocarbonyl)amino] anilino}carbonyl)oxy]methyl}phenoxy)butanoic acid (Compound No. 2 in Table 1)

Methyl 4-(3-{[({3-methoxy-4-[(2-toluidinocarbonyl)amino]anilino}carbonyl) oxy]methyl}phenoxy)butanoate(0.15 g) was hydrolysed by the method described in example 1 to give 0.07g of product as a dark powder.

Mass spectrum M+H 508

1H nmr (DMSO-d6) included the following resonances:

1.9 (m), 2H; 2.2 (s), 3H; 2.4 (t), 2H; 3.8 (s), 3H; 4.0 (t), 2H; 5.1 (s), 2H; 6.9 (m), 5H; 7.1 (m), 2H; 7.3 (m), 2H; 7.8 (d), 1H; 8.0 (d), 1H; 8.4 (s), 1H; 8.5 (s), 1H; 9.6 (s), 1H.

a) Preparation of 3-methoxy-4(N'-(2-methylphenyl)urea) nitrobenzene

2-methoxy-4-nitroaniline(16.8g) in ethyl acetate(90ml) was treated with stirring with 2-methylphenylisocyanate (16.1ml). The solution was heated to 60°C for 12 hours. The solution was then chilled to 0°C and the precipitate filtered and washed with cold ethyl acetate. This gave 3-methoxy-4(N'-(2-methylphenyl)urea)nitrobenzene (10g). 1H nmr (DMSO-d6) included the following resonances:

2.2 (s), 3H; 4.0 (s) 3H; 6.9 (t) 1H; 7.2 (m) 2H; 7.7 (d) 1H; 7.8 (s) 1H; 7.9 (d) 1H; 8.4 (d) 1H; 8.8 (s) 1H; 9.2 (s) 1H.

m/Z 302(M+H), 300(m-H).

b) Preparation of N-(4-amino-2-methoxyphenyl)-N'-(2-methylphenyl)urea)

At ambient temperature a rapidly stirred solution of 3-methoxy-4(N'-(2-methylphenyl)urea)nitrobenzene(5g) in DMF (50ml) containing 10% palladium on carbon

(500mg) was exposed to an atmosphere of hydrogen. When uptake of hydrogen had ceased the solution was filtered and the filter cake washed with dichloromethane. The combined filtrates were evaporated to dryness under reduced pressure, triturated with diethylether and filtered to give product (4.14g) as a off-white solid.

1H nmr (DMSO-d6) included the following resonances:

2.2 (s) 3H; 3.8 (s) 3H; 4.8 (s) 2H; 6.1 (d) 1H; 6.3 (s) 1H; 6.8 (t) 1H; 7.1 (m) 2H; 7.5 (d) 1H; 7.8 (d) 1H; 8.05 (s) 1H; 8.15 (s) 1H.

m/Z 272(M+H)

c) Preparation of methyl 4-(3-{[({3-methoxy-4-[(2-toluidinocarbonyl)amino] anilino}carbonyl)oxy]methyl}phenoxy)butanoate

N-(4-amino-2-methoxyphenyl)-N'-(2-methylphenyl)urea)(0.27g) was treated with the chloroformate of methyl 4-(3-hydroxymethyl)phenoxybutyrate as described in example 1 to give product (0.16g).

1H nmr (DMSO-d6) included the following resonances :

2.0 (m), 2H; 2.2 (s), 3H; 2.5 (m), 2H; 3.6 (s), 3H; 3.8 (s), 3H; 4.0 (t), 2H; 5.1 (s), 2H; 6.9 (m), 5H; 7.1 (m), 2H; 7.3 (m), 2H; 7.8 (d), 1H; 8.0 (d), 1H; 8.4 (s), 1H; 8.5 (s), 1H; 9.6 (s), 1H.

Example 5 - Preparation of 2-(3-{2[({4[2-toluidinocarbonyl)amino]anilino} carbonyl)oxy]ethyl}phenoxy)acetic acid (Compound No. 7 in Table 1)

Tertiary-butyl-2-(3-{2[({4[2-toluidinocarbonyl)amino]anilino}carbonyl)oxy]ethyl} phenoxy)ethanoate (0.5g) was hydrolysed by the method described in example 3 (0.41g)
Mass spectrum M-H 462

1H nmr (DMSO-d6) included the following resonances :

2.2 (s), 3H; 2.9 (t), 2H; 4.3 (t), 2H; 4.7 (s), 2H; 6.7 (q), 1H; 6.9 (m), 3H; 7.1 (m), 3H; 7.3 (s), 4H; 7.8 (m), 2H; 8.8 (s), 1H; 9.5 (s), 1H.

a) Preparation of t-butyl 3-(2-hydroxyethyl)phenoxyacetate

To 3-(2-hydroxyethyl)phenol (2.8g) in N-methylpyrollidinone (8ml) was added potassium carbonate (5.6g) and t-butylbromoacetate (4.4g). The mixture was stirred for 18hrs, added to water (40ml) and extracted into diethyl ether. The organic layer was washed

with brine, dried and evaporated to dryness to give t-butyl 3-(2-hydroxyethyl)phenoxyacetate (5.3g) used without further purification

1H nmr ($CDCl_3$) included the following resonances :

1.5 (s), 9H; 2.8 (t), 2H; 3.8 (q), 2H; 4.5 (s), 2H; 6.8 (m), 3H; 7.2 (t), 1H.

b) Preparation of t-butyl 2-[3-(2-{[(4-nitroanilino)carbonyl]oxy} ethyl)phenoxy]ethanoate

Tertiary-butyl 3-(2-hydroxyethyl)phenoxyacetate (2.5g) was reacted with 4-nitrophenylisocyanate (1.6g) by the method described in example 3 to give the product(2.9g)

1H nmr ($CDCl_3$) included the following resonances :

1.5 (s), 9H; 3.0 (t), 2H; 4.4 (t), 2H; 4.6 (s), 2H; 6.8 (m), 3H; 7.2 (m), 2H; 7.6 (d), 2H; 8.2 (d), 2H.

c) Preparation of t-butyl-2-(3-{2[({4[2-toluidinocarbonyl)amino]anilino} carbonyl)oxy]ethyl}phenoxy)ethanoate

t-butyl 2-[3-(2-{[(4-nitroanilino)carbonyl]oxy}ethyl)phenoxy]ethanoate (0.8g) was reduced and reacted with o-tolylisocyanate by the method described in example 2 to give the product(0.7g) as a white powder.

1H nmr (DMSO-d6) included the following resonances :

1.4 (s), 9H; 2.2 (s), 3H; 2.9 (t), 2H; 4.4 (t), 2H; 4.6 (s), 2H; 6.9 (m), 4H; 7.1 (m), 3H; 7.8 (m), 2H; 8.8 (s), 1H; 9.5 (s), 1H.

Example 6

Preparation of Compound No. 31 in Table 2

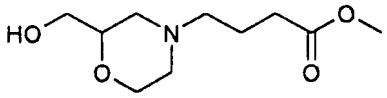
To the methyl ester of the Compound 31 (0.099g) in MeOH (1ml) was added 2N aq NaOH solution (0.08ml), and the mixture stirred at ambient temperature for 16 hrs. This was then evaporated to dryness, the residue dissolved in THF (5ml) and acidified with conc. hydrochloric acid. This solution was then adsorbed onto silica, and purified by chromatography on silica, using increasingly polar mixtures of CH_2Cl_2/MeOH (5%-20%) and the appropriate fractions evaporated to dryness to give the Compound 31 (0.054g) as an off-white solid (56%).

MS M+H 515

NMR spectrum (in DMSO-d_6) included the following resonances:

1.62(m) 2H, 1.80-2.04 (m) 2H, 2.05 (s) 3H, 2.20-2.30 (m) 7H, 2.62 (d) 2H, 2.68 (d) 2H, 3.82 (s) 3H, 4.04 (m) 3H, 6.95 (m) 2H, 7.14 (m) 2H, 7.76 (d) 1H, 7.90 (s) 1H, 8.52 (s) 1H, 8.54 (s) 1H, 8.80 (s) 1

a) Preparation of alcohol intermediate

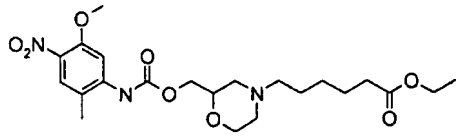


2-(Hydroxymethyl) morpholine (0.8g) was dissolved in acetonitrile (15 ml), and to this solution were added anhydrous potassium carbonate (2.85g; 3 equivalents), potassium iodide (0.025g; catalytic amount) and methyl-4-bromobutyrate (0.95 ml; 1.05 equivalents). This reaction mixture was then stirred at 60° C for 16 hours. The cooled suspension was then filtered. washing with more acetonitrile, and the filtrate concentrated under reduced pressure to give the desired alcohol as a yellow oil (1.48g; 100% yield not purified).

MS Data: M+H 218

b) Preparation of nitrophenyl intermediate

The alcohol intermediate of step 1 was reacted with 4-nitrophenylisocyanate as described in Example 2a to give the corresponding nitro intermediate of formula

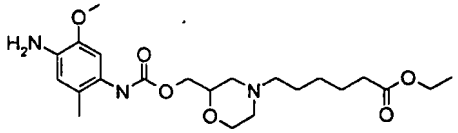


MS M+H 426

NMR spectrum (in DMSO-d_6) included the following resonances:

1.64-1.72 (m) 2H, 1.80-1.86 (m) 1H, 1.92-2.04 (m) 1H, 2.20 (s) 3H, 2.26-2.36 (m) 4H, 2.60-2.64 (m) 1H, 2.72-2.78 (m) 1H, 3.42-3.52 (m) 1H, 3.58 (s) 3H, 3.66 (m) 1H, 3.80 (m) 1H, 3.84 (s) 3H, 4.10 (d) 2H, 7.60 (s) 1H, 7.78 (s) 1H, 9.28 (s) 1H

c)Preparation of aniline intermediate



The nitro compound from (b) (0.47g) was dissolved in ethanol (10 ml) and ammonium formate (0.625g; 10 equivalents) was added. The reaction flask was flushed with

argon, and the catalyst (10% Pd/C, 0.047mg; 0.1 equivalents by weight) was then added. The reaction was heated to reflux and stirred at this temperature for 1 hour. The reaction mixture was then cooled and filtered through a bed of celite, washing through with more ethanol. The solvent was removed under reduced pressure, and the residue dissolved in ethyl acetate (50ml). This solution was then washed with water, brine, dried over anhydrous magnesium sulphate and concentrated under reduced pressure to give the above aniline as a brown oil (0.43g; 98% yield).

MS Data: M+H 438

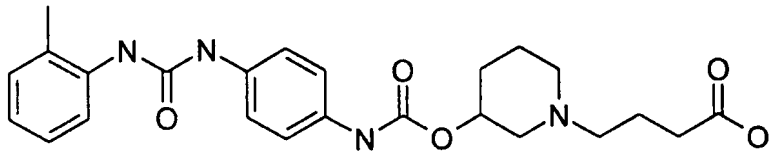
d) Preparation of Methyl Ester precursor to Compound 31

The aniline intermediate of step c was reacted with o-tolylisocyanate as described in Example 2c to yield the required methyl ester.

MS Data: M+H 529

Example 7

Preparation of Compound No. 29 in Table 2



To the methyl ester of the above (0.075g) in THF (2ml) was added a solution of $LiOH.H_20$ (0.04g) in H_20 (2ml), and the mixture stirred at ambient temperature for 16 hrs. This was acidified with conc, hydrochloric acid and evaporated to dryness. Purified by chromatography on silica, using increasingly polar mixtures of CH_2Cl_2/MeOH (5%-20%) and the appropriate fractions evaporated to dryness to give the above material (0.064g) as an off-white solid (88%).

MS M+H 455

Example 8

Using the methods of the Examples as described above, where Method A is as described in Example 1, Method B is as described in Example 2, Method C is as described in

Example 7, Method D is as described in Example 7, the following compounds whose structures are listed in Tables 1 , 2 and 3 were prepared:

Table 4

No.	Method	NMR	MS	Yield
3	A	2.3 (m), 5H, 2.8 (t) 2H, 5.2 (s) 2H, 6.8-7.4 (m), 11H, 7.9 (m) 2H, 8.9 (s) 1H, 9.6 (s) 1H	M+H 448	60%
4	A	1.5 (d) 3H, 1.9 (m), 2H, 2.2 (s) 3H, 2.2 (t) 2H, 4.0 (t) 2H, 5,7 (q), 1H, 6.8-7.3 (m), 11H, 8.8 (d) 1H, 8.9 (s) 1H, 8.9 (s) 1H, 9.5 (s) 1H	M-H 490	80%
8	A	2.2 (s) 3H, 5.2 (s) 2H, 6.6 (d) 1H, 7.9 (t) 1H, 7.1 (m) 2H, 7.4 (s) 4H, 7.6-7.9 (m) 7H, 8.9 (s) 1H, 9.6 (s) 1H	M+H 446	70%
9	A	1.9 (m) 2H, 2.1 (s) 3H, 2.2 (s) 3H, 2.4 (t), 2H, 2.8 (t) 2H, 4.0 (t) 2H, 4.2 (t) 2H, 6.8 (m) 4H, 7.1 (m) 5H, 7.3 (s) 1H, 8.8 (d) 1H, 7.85 (s) 1H, 8.6 (s) 1H, 8.9 (s) 1H	M+H 506	70%
10	B	2.2 (s) 3H, 3.2 (s) 3H 4.6 (s) 2H, 5.0 (s) 2H, 6.9 (m), 4H, 7.2 (m), 5H, 7.4 (d) 2H, 7.8 (s) 1H, 7.9 (s) 1H, 9.0 (s) 1H	M+H 464	50%
11	A	1.9 (m) 2H, 2.2 (s) 3H, 2.4 (t) 2H, 3.9 (t) 2H, 4.2 (d) 2H, 5.0 (m) 4H 5.8 (m) 1H, 6.9 (m) 4H, 7.2 (m) 5H, 7.4 (d) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 9.0 (s) 1H	M+H 518	70%
12	B	2.1 (s) 3H, 2.2 (s) 3H, 4.6 (s) 2H, 5.0 (s) 2H, 6.8-7.3 (m) 10H, 7.8 (m) 2H, 8.8 (s) 1H, 8.9 (s) 1H	M+H 464	60%
13	A	1.95 (m) 2H, 2.15 (s) 3H, 2.2 (s) 3H, 2.4 (t) 2H, 4.0 (t) 2H, 5.0 (s) 2H, 7.3 (m) 10H, 7.8 (m) 2H, 8.8 (s) 1H, 8.9 (s) 1H	M+H 492	70%
14	A	0.9 (t) 3H, 1.3 (m) 2H, 1.8 (m) 4H, 2.2 (s) 3H, 2.4 (t) 2H, 4.0 (t) 2H, 5.6 (t) 1H, 6.9 (m) 4H, 7.1 (m) 2H, 7.3 (m) 5H, 8.8 (m) 2H, 8.9 (s) 1H, 9.5 (s) 1H	M-H 518	70%

No.	Method	NMR	MS	Yield
15	A	0.9 (t) 3H, 1.3 (m) 2H, 1.8 (m) 4H, 2.2 (s) 3H, 2.4 (t) 2H, 3.1 (s) 3H, 4.0 (t) 2H, 5.6 (t) 1H, 6.8 (m) 3H, 6.9 (t) 1H, 7.1 (m) 5H, 7.4 (d) 2H, 7.8 (d) 1H 7.9 (s) 1H, 9.0 (s) 1H	M-H 532	60%
17	A	1.9 (m) 2H, 2.1 (s) 3H, 2.2 (s) 3H, 2.4 (t) 2H, 3.8 (s) 3H, 4.0 (t) 2H, 5.1 (s) 2H, 6.9 (m) 5H, 7.1 (m) 2H, 7.3 (t) 1H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H, 8.8 (s) 1H	M+H 522	70%
18	B	2.05 (s) 3H, 2.15 (s) 3H, 3.8 (s) 3H, 4.7 (s) 2H, 5.1 (s) 2H, 6.8-7.3 (m) 8H, 7.8 (d) 1H, 7.95 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H, 8.8 (s) 1H	M+H 494	70%
20	A	1.9 (m) 2H,2.2 (s) 3H, 2.4 (t) 2H, 3.8 (s) 3H, 4.0 (t) 2H, 5.0 (s) 2H, 7.0 (m) 6H, 7.4 (s) 4H, 7.8 (m) 2H, 8.9 (s) 1H, 9.6 (s) 1H	M+H 508	70%
21	A	1.9 (m) 2H, 2.1 (s) 3H, 2.2 (s) 3H, 2.4 (t) 2H, 3.05 (s) 3H, 3.8 (s) 3H, 4.0 (t) 2H, 5.1 (s) 2H, 6.9 (m) 5H, 7.1 (m) 2H, 7.3 (t) 1H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H	M+H 536	50%
22	A	1.00 (d) 3H, 2.15 (m) 2H, 2.22 (s) 3H, 2.28 (m) 1H, 3.84 (d) 2H, 5.06 (s) 2H, 6.86-7.38 (m) 11H, 7.80 (s) 1H, 7.82 (s) 1H, 8.88 (s) 1H, 9.58 (s) 1H	M+H 492	46%
23	B	2.1 (s) 3H, 2.2 (s) 3H, 3.6 (t) 2H, 3.8 (s) 3H, 4.5 (s) 2H, 5.1 (s) 2H, 6.8-7.4 (m) 8H, 7.8 (d) 2H, 7.9 (s) 1H, 8.5 (s) 1H, 8.6 (s) 1H, 8.9 (s) 1H	M+H 522	70%
24	B	2.2 (s) 3H, 3.6 (t) 2H, 4.6 (s) 2H, 5.2 (s) 2H, 6.9 (t) 1H, 7.1 (m) 2H, 7.4 (m) 8H, 7.8 (m) 2H, 8.8 (s) 1H, 9.7 (s) 1H	M+H 478	60%
25	B	2.1 (s) 3H, 2.2 (s) 3H, 3.8 (s) 3H,4.2 (m) 2H, 4.4 (m) 2H, 4.6 (m) 2H, 6.5 (m) 3H, 6. 9(m) 2H, 7.1 (m) 3H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H,	M+H 524	60%

No.	Method	NMR	MS	Yield
		8.9 (s) 1H		
26	A	1.6 (m) 4H, 2.1 (s) 3H, 2.2 (s) 3H,2.6 (m) 2H, 3.4 (s) 2H, 3.8 (s) 3H, 4.0 (m) 2H, 6. 9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H, 8.7 (s) 1H	M+H 520	80%
28	A		M+H 469	22%
29	D		M+H 455	88%
30	C		M+H 471	22%
32	C		M+H 513	25%
33	C	1.44-2.00 (m) 7H, 2.10 (s) 3H, 2.15 (m) 2H, 2.24 (s) 3H, 2.70-2.90 (m) 4H, 3.80 (s) 3H, 4.06 (m) 4H, 6.90-6.98 (m) 2H, 7.06-7.16 (m) 3H, 7.78 (d) 1H, 7.90 (s) 1H, 8.44 (s) 1H, 8.50 (s) 1H,	M+H 513	51%
34	C	1.35-1.95 (m) 7H, 2.10-2.15 (m) 4H, 2.20 (s) 3H, 2.36 (m) 2H, 2.72 (m) 2H, 4.06 (t) 2H, 6.88 (m) 1H, 7.08-7.18 (m) 3H, 7.35 (s) 4H, 7.80 (d) 1H, 8.00 (s) 1H, 9.12 (s) 1H	M+H 469	54%
35	A	1.8 (m) 6H, 2.1 (s) 3H, 2.2 (s) 3H, 2.4 (m) 2H, 2.9-3.4 (m) 6H, 3.8 (s) 3H, 4.8 (m) 1H, 6.9 (m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.5 (m) 2H, 8.6 (s) 1H	M+H 499	50%
36	C	1.32 (m) 2H, 1.54 (m) 2H, 1.70 (m) 2H, 2.10 (s) 3H, 2.24 (m) 5H, 2.70-3.50 (m) 7H, 3.80 (s) 3H, 4.02-4.18 (m) 4H, 6.88-6.96 (m) 2H, 7.06-7.18 (m) 2H, 7.76 (d) 1H, 7.92 (s) 1H, 8.44 (s) 1H, 8.52 (s) 1H, 8.88 (s) 1H	M+H 543	22%
37	A	1.5 (m) 2H, 1.9 (m) 5H, 2.1 (s) 3H, 2.2 (s) 3H, 2.3 (m) 2H, 3.0 (m) 4H, 3.5 (m) 2H, 3.8 (s) 3H, 4.0 (d) 2H, 6.9 (m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.5 (m) 2H, 8.6 (s) 1H	M+H 513	50%

No.	Method	NMR	MS	Yield
38	C	1.65 (m) 2H, 2.06 (s) 3H, 2.20-2.24 (m) 5H, 2.45 (m) 2H, 2.68 (t) 2H, 3.60 (s) 2H, 3.80 (s) 3H, 4.10 (t) 2H, 6.92 (m) 2H, 7.08-7.16 (m) 2H, 7.20-7.32 (m) 5H, 7.78 (d) 1H, 7.90 (s) 1H, 8.40 (s) 1H, 8.48 (s) 1H, 8.64 (s) 1H	M+H 549	31%
39	C	1.08-1.42 (m) 4H, 1.52-1.64 (m) 2H, 1.72-2.10 (m) 6H, 2.14 (s) 3H, 2.22 (s) 3H, 2.54 (m) 2H, 3.04-3.20 (m) 5H, 3.80 (s) 3H, 4.40 (m) 2H, 6.86-6.94 (m) 2H, 7.06-7.18 (m) 2H, 7.78 (d) 1H, 7.94 (s) 1H, 8.45 (s) 1H, 8.50 (s) 1H, 8.82 (s) 1H	M+H 541	35%
40	A	1.2-1.6 (m) 11H, 1.8 (t) 2H, 2.1 (m) 5H, 2.2 (m) 5H, 2.8 (m) 2H, 3.8 (s) 3H, 3.9 (d) 2H, 6.9 (m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.5 (m) 2H, 8.6 (s) 1H	M+H 541	30%
41	B	1.2-1.6 (m) 10H, 1.8 (m) 3H, 2.1 (s) 3H, 2.3 (s) 3H, 3.0 (m) 2H, 3.8 (s) 3H, 4.0 (m) 5H, 6.9 (m) 2H, 7.1 (m) 3H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H 8.6 (s) 1H	M+H 513	40%
42	C	1.2-1.6 (m) 10H, 1.8 (m) 3H, 2.1 (s) 3H, 2.2 (m) 5H, 2.4 (m) 1H, 2.7 (m) 1H, 3. 8 (s) 3H, 4.0 (m) 2H, 6.9 (m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.6 (s) 2H	M+H 527	80%
43	B	1.4 (m) 2H, 1.6 (m) 3H, 1.8 (m) 2H, 2.1 (s) 3H, 2.2 (s) 3H, 2.7 (t) 2H, 2.9 (m) 2H, 3.2 (m) 2H, 3.5 (m) 2H, 3.8 (s) 3H, 4.1 (t) 2H, 6. 9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H, 8.6 (s) 1H	M+H 513	70%
44	B	2.1 (s) 3H, 2.2 (s) 3H, 2.6 (t) 2H, 2.8-3.2 (m) 12H, 3.8 (s) 3H, 4.2 (m) 2H, 6. 9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H, 8.9 (s) 1H	M+H 514	80%

No.	Method	NMR	MS	Yield
45	B	1.5 (m) 4H, 1.9 (m) 1H, 2.1 (s) 3H, 2.2 (s) 3H, 3.0 (m) 2H, 3.4 (m) 4H, 3.8 (s) 3H, 4.1 (m) 4H, 6. 9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H, 8.8 (s) 1H	M+H 499	80%
46	B	1.3 (m) 2H, 1.6 (m) 2H, 1.8 (m) 4H, 2. 1 (s) 3H, 2.2 (s) 3H, 3.3 (m) 5H, 3.8 (s) 3H, 4.0 (m) 4H, 6. 9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H, 8.6 (s) 1H	M+H 513	70%
47	C		M+H 499	36%
48	C		M+H 527	63%
49	C		M+H 527	42%
50	B	2.1 (s) 3h, 2.2 (S) 3h, 2.9 (s) 3H, 3.3-3.8 (m) 10H, 3.8 (s0 3H, 4.4 (m) 2H, 6. 9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H, 8.9 (s) 1H	M+H 503	90%
51	B	2. 1 (s) 3H, 2.2 (s) 3H, 2.8-3.6 (m) 10H, 3.8 (s) 3H, 4.3 (m) 2H, 6. 9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H, 8.8 (s) 1H	M+H 500	80%
52	B	1.6 (m) 2H, 1.9 (m) 3H, 2.1 (s)3H, 2.2 (s) 3H, 3.0 (m) 2H, 3.5 (m) 2H, 3.8 (s) 3H, 4.0 (m) 2H, 4.1 (s) 2H, 6. 9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H, 8.7 (s) 1H	M+H 485	80%
53	A	1.1 (d) 3H, 2.1 (s) 3H, 2.2 (s) 3H, 2.5 (m) 10H, 3.2 (m) 1H, 3.8 (s) 3H, 4.1 (m) 2H, 6.9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8..5 (s) 1H, 8.7 (s) 1H	M+H 514	30%
54	A	1.9 (m) 2H, 2.2 (s) 3H, 2.4 (t) 2H, 3.1 (m) 2H, 4.0 (t) 4H, 5.2 (s) 1H, 6.8-7.4 (m) 10H, 7.8 (d) 1H, 8.0 (s) 1H,9.1 (s) 1H	M+H 504	80%

a) Alkyl (usually methyl or ethyl) ester intermediates (i.e. compounds of formula (I) where R^5 is an methyl or ethyl carboxylic ester) used in the process were generally obtained as described in Example 2c. The characterising data where available of the esters are set out in Table 5.

Table 5

No.	NMR	Notes	Mass Spec.
4	1.2 (t) 3H, 1.5 (d) 3H, 2.0 (m) 2H, 2.2 (s) 3H, 2.4 (m) 2H, 4.0 (t)2H, 4.1 (q) 2H, 5.7 (m) 1H, 6.8-7.1 (m) 6H, 7.3 (t) 1H, 7.4 (s) 4H, 7.8 (m) 2H, 8.8 (s) 1H, 9.5 (s) 1H		
54	2.0 (m) 2H, 2.2 (s) 3H, 2.5 (m) 2H, 3.1 (t) 2H, 3.6 (s) 3H, 4.0 (m) 4H, 5.2 (s) 2H, 6.8-7.6 (m) 10H, 7.8 (m) 2H, 8.8 (s) 1H		
8	1.3 (t) 3H, 2.2 (s) 3H, 4.2 (q) 2H, 5.1 (s) 2H, 6.7 (d) 1H, 6.9 (t) 1H, 7.1 (m) 2H, 7.4 (s) 4H,7.5-7.8 (m) 7H, 8.8 (s) 1H, 9.6 (s) 1H		M+H 474
9	1.9 (m) 2H, 2.1 (s)3H, 2.2 (s) 3H, 2.5 (m) 2H, 2.9 (t) 2H, 3.6 (s) 3H, 3.9 (t) 2H, 4.2 (t) 2H, 6.8 (m) 3H, 6.9 (t) 1H, 7.1 (m) 5H, 7.3 (s) 1H, 7.8 (m) 2H, 8.6 (s) 1H, 8.9 (s) 1H		
10	1.4 (s) 9H, 2.2 (s) 3H, 3.2 (s) 3H, 4.6 (s) 2H, 5.0 (s) 2H, 6.8 (m) 4H, 7.2 (m) 5H, 7.4 (d) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 9.0 (s) 1H	Alkylation	
11	2.1 (m) 2H, 2.2 (s) 3H, 2.5 (t) 2H, 3.6 (s) 3H, 3.8 (m) 2H, 4.2 (d) 2H, 5.1 (m) 4H, 5.9 (m) 1H, 6.5-7.3 (m) 14H, 7.6 (d) 1H	Alkylation	
12	1.4 (s) 9H, 2.1 (s) 3H, 2.2 (s) 3H, 4.6 (s) 2H, 5.1 (s) 2H, 6.8-7.3 (m) 10H, 7.8 (m) 2H, 8.8 (s) 1H, 8.9 (s) 1H		
13	2.0 (m) 2H, 2.2 (s) 3H, 2.3 (s) 3H, 2.5 (m) 2H, 3.6 (s) 3H, 4.0 (t) 2H, 5.1 (s) 2H, 6.8-7.3 (m) 10H, 7.8 (m) 2H, 8.8 (s) 1H, 8.9 (s) 1H		
14	0.9 (t) 3H, 1.3 (m) 2H, 1.8 (m) 2H, 2.0 (m) 2H, 2.2 (s) 3H, 2.5 (m) 2H, 3.6 (s) 3H, 4.0 (m) 2H, 5.6 (m) 1H, 6.9 (m) 4H, 7.1-7.2 (m) 7H, 7.8 (m) 2H, 8.8 (s)1H, 9.5 (s) 1H		

No.	NMR	Notes	Mass Spec.
15	0.9 (t) 3H, 1.3 (m) 2H, 1.8 (m) 4H, 2.2 (s) 3H, 2.4 (t) 2H, 3.1 (s) 3H, 3.7 (s) 3H,4.0 (t) 2H, 5.6 (t) 1H, 6.8 (m) 3H, 6.9 (t) 1H, 7.1 (m) 5H, 7.4 (d) 2H, 7.8 (d) 1H 7.9 (s) 1H, 9.0 (s) 1H	Alkylation	M-H 546
17	1.9 (m) 2H, 2.1 (s) 3H, 2.2 (s) 3H, 2.4 (t) 2H, 3.6 (s) 3H, 3.8 (s) 3H, 4.0 (t) 2H, 5.1 (s) 2H, 6.9 (m) 5H, 7.1 (m) 2H, 7.3 (t) 1H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H, 8.8 (s) 1H		M+H 536
18	1.4 (s) 9H,21. (s) 3H, 2.2 (s)3H, 3.8 (s) 3H, 4.6 (s) 2H, 5.1 (s) 2H, 6. 9(m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H, 8.8 (s) 1H		
20	2.0 (m) 2H, 2.2 (s) 3H, 3.6 (s) 3H, 3.8(s) 3H, 4.0 (t) 2H, 5.0 (s0 2H, 6.8-7.2 (m) 6H, 7.4 (s) 4H,7.8 (m) 2H, 8.9 (s) 1H, 9.5 (s) 1H		M+H 522
21	1.9 (m) 2H, 2.1 (s) 3H, 2.2 (s) 3H, 2.4 (t) 2H, 3.05 (s) 3H, 3.6 (s) 3H, 3.8 (s) 3H, 4.0 (t) 2H, 5.1 (s) 2H, 6.9 (m) 5H, 7.1 (m) 2H, 7.3 (t) 1H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H	Alkylation	M+H 550
22	1.00 (d) 3H, 2.22 (s) 3H, 2.30 (m) 3H, 3.60 (s) 3H, 3.86 (d) 2H, 5.06 (s) 2H, 6.85-6.98 (m) 4H, 7.06-7.18 (m) 2H, 7.30 (t) 1H, 7.36 (s) 4H, 7.80 (s) 1H, 7.82 (s) 1H, 8.86 (s) 1H, 9.58 (s) 1H		M+H 506
23	1.4 (s) 9H, 2.1 (s) 3H, 2.2 (s) 3H, 2.5 (m) 2H, 3.6 (t) 2H, 3.9 (s) 3H, 4.5 (s)3H, 5.1 (s0 3H, 6.9 (m) 2H, 7.2 (m) 2H, 7.4 (m) 4H, 7.8 (d) 1H, 8.0 (s0 1H, 8.5 (s0 1H, 8.6 (s) 1H, 8.8 (s) 1H		M-H 576
24	1.3 (s) 9H, 2.2 (s) 3H, 2.5 (m) 2H, 3.6 (m) 2H, 4.5 (s) 2H, 5.1 (s) 2H, 6.9-7.3 (m) 11H, 7.8 (m) 2H, 8.9 (s) 1H, 9.6 (s) 1H		M-H 532
25	1.4 (s) 9H, 2.1 (s)3H, 2.2 (s) 3H, 3. 8 (s) 3H, 4.2 (m) 2H, 4.4 (M) 2H, 4.6 (s) 3H, 6.5 (m) 3H, 6.9 (m) 2H, 7.1 (m) 3H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H, 8.8 (s) 1H		M+H 580
26	1.6 (m) 4H, 2.1 (s) 3H, 2.2 (s) 3H, 2.6 (m) 2H, 3.6 (s) 3H, 3.65 (s) 2H, 3. 8(s) 3H, 4.0 (m) 2H, 6.8 (m) 2H, 7.1 (m) 6H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H, 8.6 (s) 1H		M+H 534

No.	NMR	Notes	Mass Spec.
28	1.00-1.24 (m) 1H, 1.42-2.10 (m) 6H, 2.22 (s) 3H, 2.25-2.42 (m) 4H, 3.24-3.40 (m) 4H, 3.60 (s) 3H, 3.88-4.02 (m) 2H, 6.90 (t) 1H, 7.14-7.18 (m) 2H, 7.36 (s) 4H, 7.80 (d) 1H, 7.88 (s) 1H, 8.96 (s) 1H, 9.44 (s) 1H		M+H 483
29			M+H 469
30			M+H 485
31			M+H 529
32			M+H 527
33			M+H 541
34			M+H 497
35			M+H 513
36	1.18 (t) 3H, 1.20-1.30 (m) 2H, 1.36-1.46 (m) 2H, 1.46-1.58 (m) 2H, 1.80 (t) 1H, 1.98 (m) 1H, 2.10 (s) 3H, 2.22 (s) 3H, 2.24 (m) 4H, 2.60-2.78 (m) 2H, 3.46 (m) 1H, 3.62 (m) 1H, 3.78 (m) 1H, 3.82 (s) 3H, 4.00-4.08 (m) 4H, 6.86-6.96 (m) 2H, 7.04-7.18 (m) 2H, 7.78 (d) 1H, 7.90 (s) 1H, 8.40 (s) 1H, 8.48 (s) 1H, 8.88 (s) 1H		M+H 571

No.	NMR	Notes	Mass Spec.
37			M+H 527
38	($CDCl_3$) 1.78-1.84 (m) 2H, 2.20 (s) 3H, 2.28 (s) 3H, 2.38 (t) 2H, 2.56 (t) 2H, 2.78 (t) 2H, 3.62 (s) 3H, 3.63 (s) 2H, 3.78 (s) 3H, 4.22 (t) 2H, 6.18 (s) 1H, 6.56 (m) 1H, 6.92 (s) 1H, 7.16 (m) 1H, 7.20-7.36 (m) 7H, 7.44 (s) 1H, 7.56 (d) 1H, 7.92 (s) 1H		M+H 563
39			Not isolated. Formed gel on column
40	1.1 (t) 3H,1.2-1.6 (m) 11H, 1.8 (t) 2H, 2.1 (m) 5H, 2.2 (m) 5H, 2.8 (m) 2H, 3.8 (s) 3H, 3.9 (d) 2H, 4.1 (q) 2H, 6.9 (m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.5 (m) 2H, 8.6 (s) 1H		
41	1.1-1.4 (m) 6H, 1.4 (s) 9H, 1.6 (m) 4H, 1.8 (m) 3H, 2.1 (s) 3H, 2.3 (s) 3H, 3.0 (m) 2H, 3.8 (s) 3H, 4.0 (m) 5H, 6.9 (m) 2H, 7.1 (m) 3H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H 8.6 (s) 1H		M-H 567
42			M+H 541
43			M+H 569
44	1.4 (s0 9H, 2.1 (s) 3H, 2.2 (s) 3H, 2.2-2 6 (m) 12H, 3.8 (s) 3H, 4.1 (t) 2H, 6.9 (m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H, 8.7 (s) 1H		M+H 570
45			M+H 555
46			M+H 569

No.	NMR	Notes	Mass Spec.
47	1.16-1.24 (m) 5H, 1.58-1.66 (m) 3H, 1.96 (m) 1H, 2.08 (s) 3H, 2.18-2.26 (m) 7H, 2.82-2.86 (m) 2H, 3.80 (s) 3H, 4.00-4.08 (q) 2H, 4.12 (t) 2H, 6.88-6.94 (m) 2H, 7.06-7.18 (m) 2H, 7.78 (d) 1H,7.92 (s) 1H, 8.40 (s) 1H, 8.48 (s) 1H, 8.70 (s) 1H		M+H 527
48			M+H 555
49			M+H 555
50			M+H 559
51	1.4 (s) 9H, 2.1 (s) 3H, 2.2 (s) 3H, 2.5 (m) 10H, 3.0 (s) 2H, 3.8 (s) 3H, 4.1 (m) 2H, 6.9 (m) 2H, 7.1 (m) 2H, 7.8 (d) 1H, 7.9 (s) 1H, 8.4 (s) 1H, 8.5 (s) 1H, 8.7 (s) 1H		M+H 556
52			M-H 539
53			M-H 540

In the above Table, the compound nos refer to the acids which were ultimately derived from the methyl esters. Examples with the note 'alkylation' had the appropriate nitro intermediate alkylated as described in Example 2b.

ai) The methyl ester of Compound 3 in Table 1 was obtained from a urea carbamate ester intermediate -ureidoaniline + chloroformate using a method analogous to that described in Example 1

MS M+H 462

NMR spectrum (in DMSO-d_6) included the following resonances:

2.2 (s) 3H, 2.7 (t) 2H, 2.9 (t) 2H, 3.6 (s) 3H, 5.1 (s) 2H, 6.9 (m) 1H, 7-7.4 (m) 8H, 7.8 (m) 2H, 8.8 (s) 1H, 9.4 s) 1H

b) Details of the intermediate anilines of formula (VI) are set out in Table 6. In this Table, the method indicates the following:

Y^1	$Fe/NH_4Cl/EtOH/H_2O$	As Ex 2c
Y^2	$HCO_2NH_4/Pd/C/EtOH$	As Ex 6c
Y^3	$H_2/Pd/C/EtOH$	As Ex 4b

The compound No. refers to the Compound of formula (I) which was ultimately derived from the intermediate.

Table 6

No.	Method	NMR	MS
22	Y^1	1.00 (d) 3H, 2.30 (m) 3H, 3.60 (s) 3H, 3.82 (d) 2H, 4.76 (m) 2H, 5.04 (s) 2H, 6.44 (m) 2H, 6.86 (m) 1H, 6.94 (m) 2H, 7.06 (m) 2H, 7.28 (t) 1H, 9.16 (s) 1H	M+H 373
28	Y^1		M+H 350
29	Y^1		M+H 336
30	Y^1		Not Isolated
31	Y^1		Not Isolated
32	Y^1		Not Isolated
33	Y^1		Not Isolated
34	Y^1		Not Isolated
36	Y^2		M+H 438
38	Y^1		M+H 430
39	Y^2		M+H 422
47	Y^3		M+H 394
48	Y^3		M+H 422
49	Y^3		M+H 422

c) The above described anilines were obtained from the corresponding nitro compounds of formula (XIV) as set out above using methods analogous to that of Example 2a. Data for the nitro compounds is set out in Table 7.

Table 7

No.	NMR	Mass spec.
4	1.2 (t) 3H, 1.6 (d) 3H, 2.1 (m) 2H, 2.5 (t) 2H, 4.0 (t) 2H, 4.2 (q) 2H, 5.9 (q) 1H, 6.8 (q) 1H, 6.9 (m) 2H, 7.1 (s) 1H, 7.3 (m) 2H, 7.5 (d) 2H, 8.2 (d) 2H	
8	1.3 (t) 3H, 4.2 (q) 2H, 5.2 (s) 2H, 6.6 (d) 1H, 7.5 (m) 2H,7.8 (m) 5H, 8.2 (d) 2H	
9	2.1 (m) 2H, 2.3 (s) 3H, 2.5 (t) 2H, 3.0 (t) 2H, 3.7 (s) 3H, 4.0 (t) 2H, 4.4 (t) 2H, 6.8 (m) 4H, 7.2 (d) 1H, 8.1 (m) 3H	
10	1.4 (s) 9H, 4.6 (s) 2H, 5.2 (s) 2H, 6.8 (q) 1H, 7.0 (s) 1H, 7.05 (d) 1H, 7.3 (t) 1H, 7.7 (d) 2H, 8.2 (d) 2H	
11	2.1 (m) 2H, 2.5 (t) 2H, 3.7 (s) 3H, 4.0 (t) 2H, 4.4 (m) 2H, 5.2 (m) 4H, 5.9 (m) 1H, 6.9 (m) 3H,. 7.2 (m) 1H, 7.5 (d) 2H, 8.2 (d) 2H	
12	1.5 (s) 9H, 2.3 (s) 3H, 4.5 (s) 2H, 5.2 (s) 2H, 6.7 (s) 1H, 6.9 (q) 1H, 7.0 (s) 1H, 7.05 (d) 1H, 7.3 (t) 1H, 8.1 (m) 2H, 8.3 (d) 1H	
13	2.1 (m) 2H, 2.3 (s) 3H, 2.5 (t) 2H, 3.7 (s) 3H, 4.0 (t) 2H, 5.2 (s)2H, 6.8-7.1 (m) 4H, 7.3 (t) 1H, 8.1 (m) 2H, 8.2 (d) 1H	
14	1.2 (t) 3H, 1.4 (m) 2H, 1.8 (m) 2H, 2.0 (m) 2H, 2.1 (m)2H, 2.5 (m) 2H, 3.7 (s) 3H, 4.0 (t) 2H, 5.7 (m) 1H, 6.8 (q) 1H, 6.9 (m) 2H, 7.2 (m) 2H, 7.5 (d) 2H, 8.1 (d) 2H	
15	0.9 (t) 3H, 1.3 (m) 2H, 1.8 (m) 2H, 2.2 (m) 2H, 2.5 (m) 2H, 3.4 (s) 3H, 3.7 (s) 3H, 4.0 (t) 2H, 5.7 (m) 2H, 6.8 (m) 3H, 7.2 (m) 1H, 7.5 (d) 2H, 8.2 (d) 2H	
17	2.1 (m) 2H, 2.2 (s) 3H, 2.5 (t) 2H, 3.7 (s) 3H, 4.0 (s) 3H, 4.05 (t) 2H, 5.2 (s0 2H, 6.7 (s) 1H, 6.9 (m) 3H, 7.3 (t) 1H, 7.8 (s) 1H, 8.0 (s) 1H	
18	1.5 (s) 9H, 1.6 (s) 3H, 2.2 (s) 3H, 4.0 (s) 3H, 4.5 (s) 2H, 5.2 (s) 2H, 6.7 (s) 1H, 6.9 (m) 1H, 7.0 (s) 1H, 7.05 (d) 1H, 7.3 (t) 1H, 7.8 (s) 1H, 8.0 (s) 1H	

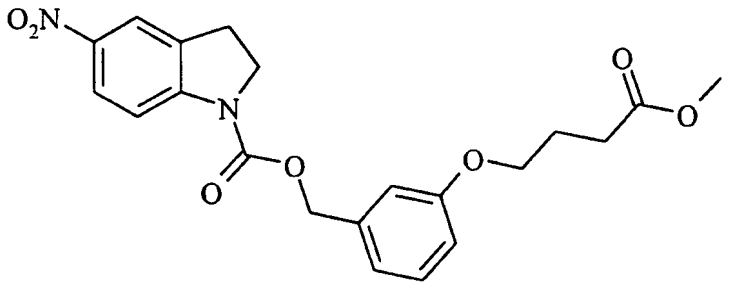
No.	NMR	Mass spec.
20	2.0 (m) 2H, 3.6 (s) 3H, 3.7 (s) 3H, 4.0 (t) 2H, 5.1 (s) 2H, 7.0 (m) 3H, 7.7 (d)2H, 8.2 (d) 2H	
21	2.1 (m) 5H, 2.5 (t) 2H, 3.2 (s) 3H, 3.7 (s) 3H, 3.9 (s) 3H, 3.95 (m) 2H, 5.1 (s) 2H, 6.8 (m) 4H, 7.2 (m) 1H, 7.7 (s) 1H	
22	1.00 (d) 3H, 2.22-2.36 (m) 3H, 3.58 (s) 3H, 3.82 (m) 2H, 5.16 (s) 2H, 6.88 (d) 1H, 7.00 (m) 2H, 7.28 (t) 1H, 7.68 (m) 2H, 8.20 (m) 2H, 10.47 (s) 1H	M-H 401
23	1.5 (s) 9H, 2.2 (s) 3H, 2.5 (t) 2H, 3.8 (t) 2H, 4.0 (s) 3H, 4.6 (s) 2H, 5.2 (s) 2H,6.8 (s) 1H, 7.3 (m) 4H, 7.8 (s) 1H, 8.0 (s) 1H	
24	1.4 (s) 9H, 2.6 (t) 2H, 3.7 (t) 2H, 4.6 (s) 2H, 5.3 (s) 2H, 7.3 (m) 5H, 7.6 (d) 2H, 8.2 (d)2H	
25		M-H 475
26	1.7 9m) 4H, 2.2 (s) 3H, 2.6 (m) 2H, 3.6 (s) 2H, 3.7 (s) 3H, 4.0 (s) 3H, 4.2 (m) 2H, 6.6 (s)1H, 7.4 (q) 4H, 7.8 (s) 1H, 8.0 (s) 1H	
28	1.02-1.10 (m) 1H, 1.38-1.46 (m) 1H, 1.60-1.72 (m) 4H, 1.76-1.96 (m) 3H, 2.24-2.34 (m) 4H, 2.60-2.82 (m) 2H, 3.58 (s) 3H, 4.02 (m) 2H, 7.66 (m) 2H, 8.20 (m) 2H, 10.34 (s) 1H	M+H 380
29	($CDCl_3$) 1.56-1.66 (m) 1H, 1.70-1.86 (m) 4H, 2.32-2.56 (m) 8H, 2.62-2.66 (m) 1H, 3.66 (s) 3H, 4.94 (m) 1H, 7.54 (m) 2H, 8.20 (m) 2H	M+H 366
30	1.62-1.72 (m) 2H, 1.80-1.86 (m) 1H, 1.94-2.04 (m) 1H, 2.24-2.34 (m) 4H, 2.60-2.64 (m) 1H, 2.72-2.78 (m) 1H, 3.48 (m) 1H, 3.58 (s) 3H, 3.68 (m) 1H, 3.80 (m) 1H, 4.12 (d) 2H, 7.66 (m) 2H, 8.18 (m) 2H, 10.46 (s) 1H	M+H 382
31	1.64-1.72 (m) 2H, 1.80-1.86 (m) 1H, 1.92-2.04 (m) 1H, 2.20 (s) 3H, 2.26-2.36 (m) 4H, 2.60-2.64 (m) 1H, 2.72-2.78 (m) 1H, 3.42-3.52 (m) 1H, 3.58 (s) 3H, 3.66 (m) 1H, 3.80 (m) 1H, 3.84 (s) 3H, 4.10 (d) 2H, 7.60 (s) 1H, 7.78 (s) 1H, 9.28 (s) 1H	M+H 426
32	1.00-1.08 (m) 1H, 1.38-1.46 (m) 1H, 1.56-1.68 (m) 4H, 1.70-1.96 (m) 3H, 2.20 (s) 3H, 2.22-2.34 (m) 4H, 2.64 (m) 1H, 2.80	M+H 424

No.	NMR	Mass spec.
	(m) 1H, 3.56 (s) 3H, 3.84 (s) 3H, 3.92-4.04 (m) 2H, 7.60 (s) 1H, 7.78 (s) 1H, 9.16 (s) 1H	
33	0.94-1.02 (m) 1H, 1.18 (t) 3H, 1.42-1.98 (m) 8H, 2.20-2.42 (m) 7H, 2.60-2.78 (m) 2H, 3.84 (s) 3H, 4.06 (q) 2H, 4.16 (t) 2H, 7.62 (s) 1H, 7.80 (s) 1H, 9.12 (s) 1H	M+H 438
34	0.96-1.04 (m) 1H, 1.16 (t) 3H, 1.38-1.94 (m) 7H, 2.02-2.40 (m) 5H, 2.72-2.74 (m) 2H, 4.02 (q) 2H, 4.16 (t) 2H, 7.66 (m) 2H, 1.18 (m) 2H, 10.34 (s) 1H	M+H 394
35		M+H 410
36	1.16 (t) 3H, 1.26 (m) 2H, 1.42 (m) 2H, 1.54 (m) 2H, 1.80 (m) 1H, 1.98 (m) 1H, 2.18 (s) 3H, 2.22-2.32 (m) 4H, 2.64 (m) 1H, 2.78 (m) 1H, 3.48 (m) 1H, 3.70 (m) 1H, 3.80 (m) 1H, 3.84 (s) 3H, 4.02 (q) 2H, 4.14 (d) 2H, 7.60 (s) 1H, 7.80 (s) 1H, 9.28 (s) 1H	M+H 468
37		M+H 424
38		M+H 460
39		M+H 452
40		M+H 466
41		M+H 466
42		M+H438
43	1.3 (m) 4H, 1.5 (s) 9H, 1.7 (m) 5H, 2.0 (t) 2H, 2.2 (s) 3H, 2.4 (t) 2H, 2.6 (t) 2H, 2.9 (m) 2H, 4.0 (s) 3H, 4.2 9t) 2H, 6.6 (s0 1H, 7.8 (s) 1H, 8.0 (s) 1H	
44		M+H 467
45		M+H 452
46	Used without purification or characterisation	
47	1.10-1.22 (m) 5H, 1.56-1.64 (m) 3H, 1.90-2.02 (m) 2H, 2.18-2.22 (m) 5H, 2.58 (t) 2H, 2.84 (m) 2H, 3.82 (s) 3H, 4.04 (q) 2H, 4.20 (t) 2H, 7.58 (s) 1H, 7.76 (s) 1H, 9.22 (s) 1H	M+H 424
48		M+H 452

No.	NMR	Mass spec.
49		M+H 452
50		M+H 456
51	1.4 (s) 9H, 2.2 (s) 3H, 2.6 (m) 8H, 2.7 (t) 2H, 3.1 (s) 2H, 4.0 (s) 3H, 4.2 (t) 2H, 6.9 (s) 1H, 7.8 (s) 1H, 8.0 (s) 1H	
52		M+H 438
53		M+H 439

Again, the compound No. column refers to the compound of formula (I) ultimately obtained from this intermediate.

ci) In the case of the nitro compound used in the preparation of compound 54 in Table 3, (i.e. the compound of formula



a modified route was used.

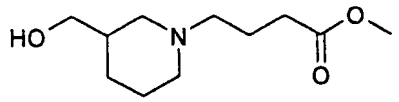
To methyl 4-(3-hydroxymethyl)phenoxybutyrate (1.12g) in dichloromethane (6ml) was added 20% phosgene in toluene (12ml) and the mixture allowed to stand for 18hrs, evaporated and the residue in dichloromethane (15ml) added to 4-nitroindoline (0.82g) in pyridine (2ml) and the mixture stirred overnight, evaporated to dryness and partitioned between aqueous acid and diethyl ether. A crystalline material precipitated and was filtered, washed with ether and dried to give the above (0.8g)

NMR

2. 0 (m) 2H, 2.4 (m) 2H, 3.2 (t) 2H, 3.6 (s) 3H, 4.0 (t) 2H, 4.1 9t) 2H, 5.2 (s) 2H, 6.9 (m) 3H, 7.3 (t) 1H, 7.8 (m) 1H, 8.1 (m) 2H

Alcohol intermediates (of general formula (XIV) above) used in the preparation of the nitro compounds were prepared by various methods. These are outlined below or summarised in Table 8.

d1) Alcohol for use in the Preparation of Compound No. 28 in Table 1

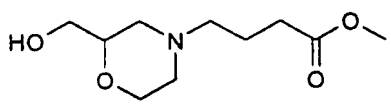


Piperidine methanol (0.5g) was dissolved in dichloromethane (10 ml) and triethylamine (0.64 ml; 1.05 equivalents) was added, followed by methyl-4-bromobutyrate (0.6 ml; 1.05 equivalents). The resulting solution was stirred at room temperature for 16 hours, then diluted with a further 40 ml dichloromethane and washed with water (25 ml). The organic solution was dried using phase separating paper and concentrated under reduced pressure. Purification on a silica Bond Elut column using dichloromethane/methanol mixtures of increasing polarity as eluent gave the desired alcohol (Example 61d) as a yellow oil (0.309g; 33% yield).

MS Data: M+H 216

NMR Data: **($CDCl_3$)** 1.20-1.34 (m) 1H, 1.58-1.70 (m) 2H, 1.70-1.90 (m) 4H, 2.04 (m) 1H, 2.14 (m) 1H, 2.26 (m) 1H, 2.36-2.44 (m) 4H, 2.66 (m) 1H, 2.84 (m) 1H, 3.56 (m) 1H, 3.66 (m) 1H, 3.68 (s) 3H,

d2) Alcohol for use in the Preparation of Compound No. 30 in Table 1

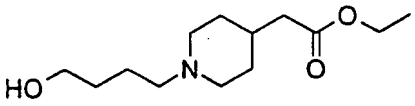


2-(Hydroxymethyl) morpholine (0.8g) was dissolved in acetonitrile (15 ml), and to this solution were added anhydrous potassium carbonate (2.85g; 3 equivalents), potassium iodide (0.025g; catalytic amount) and methyl-4-bromobutyrate (0.95 ml; 1.05 equivalents).

This reaction mixture was then stirred at 60^0 C for 16 hours. The cooled suspension was then filtered, washing with more acetonitrile, and the filtrate concentrated under reduced pressure to give the desired alcohol (Example 63d) as a yellow oil (1.48g; 100% yield not purified).

MS Data: M+H 218

d3) Alcohol for use in the Preparation of Compound No. 48 in Table 1



Method exactly in method d2, but using the alkyl chloride in place of the alkyl bromide.

MS Data: (EI+) M+ 243

d4) Alcohol for use in the Preparation of Compound No. 4 in Table 1

To 3-hydroxyacetophenone (7g) in NMP (70ml) was added potassium carbonate (13.8g) and potassium iodide (2g), followed by methyl-4-bromobutyrate (6.2ml) and the mixture stirred for 18hrs, then added to water (200ml) and extracted with ethyl acetate. The organic extracts were wshed with brine and evaporated to dryness, purified by chromatography on silica (hexane/ethyl acetate) and the appropriate fractions evaporated to dryness. 1g of this material was dissolved in ethanol and sodium borohydride (0.16g) was added and the mixture stirred for 18hrs, evaporated , and partitioned between dilute acid and diethyl ether. The organic layer was separated, dried and evaporated and the residue purified by chromatography on silica (10% ethyl acetate in hexane increasing to 90%). The aapropriate fractions evaporated to dryness gave an approx. 50:50 mixture of ethyl & methyl 4-(3-[1-hydroxy]ethyl)phenoxybutyrate.

NMR

1.2 (t) 1.5H ethyl ester , 1.5 (d) 3H, 2.1 (m) 2H, 2.5 (m) 2H, 3.7 (s) 1.5H methyl ester, 4.0 (t) 2H, 4.1 (q) 1H, ethyl ester, 4.9 (m) 1H, 6.8 (d) 1H, 6.9 (s) 2H, 7.2 (m) 1H.

d5) Alcohol for use in the Preparation of Compound No. 23

To 1,3 benzenedimethanol (1.4g) in THF (10ml) added t-butylacrylate (2g) followed by a 2 drops of benzyltrimethylammonium hydroxide solution. The mix stirred for 1hr., evaporated and purified by chromatography on silica using an increasingly polar mixture of hexane/ethyl aceate to give after evaporation of the appropriate fractions 0.55g of t-butyl (3-hydroxymethyl)benzyloxypropionate as an oil.

M+H 267

d6) Alcohol for use in the Preparation of Compound No. 35

To 4-hydroxypiperidine (2g) in DMf (35ml) was added potassium carbonate (8.2g) and methyl 4-bromobutyrate (2.9ml). The mix was stirred at 70C for 8hrs and then cooled, and partitioned between ethyl acetate and water, the organic layer washed with brine, dried and evaporated to dryness. The residue has a consistent M+H and was used without further purification or characterisation.

d7) Alcohol for use in the Preparation of Compound No. 41

To 4-(3-hydroxypropyl)pyridine (1.4g) in acetonitrile (10ml) was added t-butyl bromoacetate (2g) and the mixture allowed to stand for 24 hrs., and evaporated. The residue was dissolved in methanol and hydrogenated at atmospheric pressure in the presence of 10% palladium on carbon catalyst at 55C for 16 hrs. The mix was cooled, filtered and evaporated to give t-butyl 4-(3-hydroxypropyl)piperidinylacetate M+H 258

d8) Alcohol for use in the Preparation of Compound No. 43

To 4-(2-hydroxyethyl)piperidine (1.29g) in acetonitrile (5ml) was added t-butyl acrylate (1.28g) and the mixture allow to stand for 18hrs, evaporated to give t-butyl 4-(2-hydroxyethyl)piperidinylpropionate M+H 258

d9) Alcohol for use in the Preparation of Compound No. 25

To 3-(hydroxyethoxy)phenol (CAS49650-88-6) (1.54g) in N-methylpyrollidinone (3ml) was added potassium carbonate (2.8g) and t-butylbromoacetate (1.95g) and the mix stirred for 18hrs, then added to a mixture of brine and diethyl ether. The organic layer was washed with brine, dried and evaporated to dryness and the residue purified by

chromatography using an increasingly polar mixture of hexane / ethyl acetate to give t-butyl 3-(hydroxyethoxy)phenoxyacetate M+H 269

d10) Alcohol for use in the Preparation of Compound No. 26 in Table 1

To methyl 4-iodophenylacetate (27g) in acetonitrile (300ml) were stirred and palladium chloride (0.17g), copper (I) iodide (0.37g), triphenylphosphine (0.51g) , 3-butyn-1-ol (8.85g) and triethylamine (20ml) were added and the mixture stirred under an inert atmosphere in the absence of light for 18hrs. and then the solvent removed by evaporation and the residue partitoned between water and ethyl acetate, the organic layer removed, dried and evaporated to dryness. The residue was purified by chromatography on silica using an increasingly polar mixture of ethyl acetate/hexane. The appropriate fractions evaporated to dryness gave methyl 4-(4-hydroxybut-3-ynyl)phenylacetate (18.6g)

This was reduced in ethanol(250ml) using Pd/C catalyst (5%,2g) under an atmosphere of hydrogen gas at a pressure of 3 atmospheres for 1hr, filtered and evaporated to dryness to give methyl 4-(4-hydroxybutyl)phenylacetate (18g) as a yellow oil used without further purification or characterisation.

Table 8

No.	Source/method	n.m.r	Mass Spec.
3	CAS 62876-42-0		
8	CAS 99289-68-6		
14	As Ex 1a using CAS 134154-43-1		M+H 267
20	As Ex 1a using CAS 4383-06-6		M+NH4 272
22	As d6	1.00 (d) 3H, 2.22-2.34 (m) 3H, 3.60 (s) 3H, 3.82 (m) 2H, 4.44 (d) 2H, 5.12 (t) 1H, 6.76 (d) 1H, 6.86 (m) 2H, 7.2 (t) 1H,	M+H 239

No.	Source/method	n.m.r	Mass Spec.
28	d1	($CDCl_3$) 1.20-1.34 (m) 1H, 1.58-1.70 (m) 2H, 1.70-1.90 (m) 4H, 2.04 (m) 1H, 2.14 (m) 1H, 2.26 (m) 1H, 2.36-2.44 (m) 4H, 2.66 (m) 1H, 2.84 (m) 1H, 3.56 (m) 1H, 3.66 (m) 1H, 3.68 (s) 3H,	M+H 216
29	d2	($CDCl_3$) 1.44-1.60 (m) 3H, 1.74-1.86 (m) 3H, 2.20 (t) 1H, 2.32-2.58 (m) 8H, 3.66 (s) 3H, 3.82 (m) 1H	M+H 202
30	d2		M+H 218
33	d2		M+H 230
36	d2		M+H 260
37	As d6		M+H 216
38	d2		M+H 252
39	d2		M+H 244
40	As d6		M+H 258
42	As d6		M+H 230
44	As d8		M+H 259
45	As d6		M+H 244
46	As d7		M+H2 58
47	d2		M+ 215
48	d3		M+ 243
49	d3		M+ 243
50	As d5		M+H 248
51	As d6		M+H 245

No.	Source/method	n.m.r	Mass Spec.
52	As d6		M+H 230
53	As d6		M+H 231

Example 9

The compounds of the invention or pharmaceutically acceptable salts thereof may be formulated into tablets together with, for example, lactose Ph.Eur, Croscarmellose sodium, maize starch paste (5% w/v paste) and magnesium stearate for therapeutic or prophylactic use in humans. The tablets may be prepared by conventional procedures well known in the pharmaceutical art and may be film coated with typical coating materials such as hydroxypropylmethylcellulose.

In Vitro and In Vivo Assays

The following abbreviations are used. Suitable sources of materials are listed below.

MOLT-4 cells - human T-lymphoblastic leukaemia cells (European Collection of Animal Cell Cultures, Porton Down).

Fibronectin - purified from human plasma by gelatin-sepharose affinity chromatography according to the methods described in E.Nengvall, E.Ruoslahti, Int. J. Cancer, 1977, 20, pages 1-5 and J. Forsyth et al, Methods in Enzymology, 1992, 215, pages 311-316).

RPMI 1640 - cell culture medium. (Life technologies, Paisley UK).

PBS - Dulbecco's phosphate buffered saline (Life Technologies).

BSA - Bovine serum albumin, fraction V (ICN, Thame, UK).

CFA - Complete Freund's Adjuvant (Life Technologies).

In the following assays and models references to compound(s) refers to the compounds of formula (I) according to the present invention.

1.1 In vitro assay :

MOLT-4 cell/ Fibronectin adhesion assay.

The MOLT-4 cell /fibronectinadhesion assay was used to investigate the interaction of the integrin α_4-$\beta_1$expressed on the MOLT-4 cell membrane with fibronectin. Polystyrene 96 well plates were coated overnight at 4°C with fibronectin, 100 µl of 10 µg/ml in PBS. Non-specific adhesion sites were blocked by adding 100 µl BSA, 20 mg/ml. After incubating for

1 h at room temperature, the solutions were aspirated. MOLT-4 cells suspended in serum-free RPMI-1640 medium 2E6 cells/ml (50 µl) and solutions of compound diluted in the same medium (50 µl) were added to each well. After incubation for 2 h at 37°C in a humidified atmosphere of 5% (v/v) CO_2, non-adherent cells were removed by gentle shaking followed by vacuum aspiration. Adherent cells were quantified by a colorimetric acid phosphatase assay. To each well was added 100 µl p-nitrophenyl phosphate (6 mg/ml) in 50 mM sodium acetate buffer, pH 5.0, containing 1% Triton X-100. After incubation for 1 h at 37°C, 50 µl sodium hydroxide (1M) was added to each well and the absorbance 405 nm was measured on a microplate spectrophotometer. Compounds which inhibited adhesion gave a lower absorbance reading. Standard, control and test conditions were assayed in triplicate. Percentage inhibition was calculated with respect to total (no inhibitor) and non-specific (no fibronectin) standards on each plate.

1.2 In-vivo Inflammation Models

Activity of a compound can be tested in the following models.

1.2.1 Ovalbumin Delayed type Hypersensitivity in mice

Balb/c female mice (20-25g) are immunised on the flank with an 1:1 (v/v) emulsion of ovalbumin (2 mg/ml) with CFA. Seven days later the mice are challenged by subplantar injection of 1% heat aggregated ovalbumin in saline (30 µl) into the right hind foot pad. Swelling of the foot develops over a 24 hour period following which foot pad thickness is measured and compared with the thickness of the contralateral uninjected foot. The percentage increase in foot pad thickness is calculated. Compounds are dosed orally by gavage to groups of 5 mice at doses ranging from 0.001 mg/kg to 100 mg/kg. Inhibition of the inflammatory response is calculated comparing vehicle treated animals and compound treated groups.

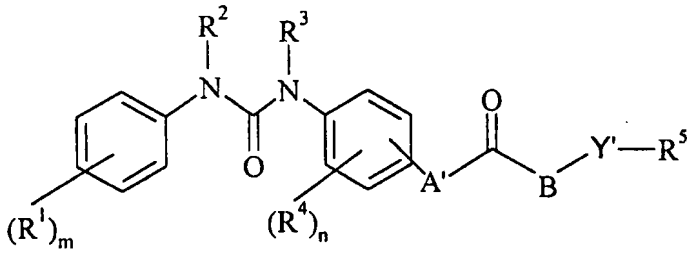
1.2.2. Collagen-induced arthritis in mice

DBA/1 male mice are immunised with 0.1ml of an emulsion prepared from equal volumes of bovine collagen type II in 0.05M acetic acid (2 mg/ml) and CFA. This mixture is injected at the base of the tail. Twenty days later compounds are dosed orally by gavage at doses ranging from 0.001mg/kg/day to 100 mg/kg/day. On the day following the first dose, each animal receives an intra-peritoneal booster injection of 0.1ml of collagen type II in acetic acid. The mice are assessed for the incidence and severity of arthritis in all four limbs for up

to 28 days. Inhibition of arthritis is calculated by comparing vehicle treated and compound treated mice.

Claims:

1. A compound of formula (I)



(I)

wherein

A' is NH or NR^6, where R^6 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkanoyl or C_{1-6}alkoxycarbonyl;

B is oxygen or sulphur;

Y' is a linker group comprising an optionally substituted hydrocarbyl chain which is optionally interposed by one or more heteroatoms independently selected from oxygen, nitrogen and sulphur and/or by a monocyclic or bicyclic ring system; or linker group Y' and A' can be taken together to form a 5 to 7 membered heterocyclic ring, optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

m is from 0 to 5;

n is from 0 to 4;

R^1 and R^4 are each independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6} alkylamino, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, N,N-di-[(C_{1-6}alkyl]carbamoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_tOH$ where t is 1 or 2, $-CO_2R^a$ and $CONR^aR^b$ where R^a and R^b are independently hydrogen or C_{1-6} alkyl or one of R^4 can be taken together with A to form a 5 to 7 membered heterocyclic ring optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino,

nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-3} alkanoyl or C_{1-6} alkoxycarbonyl; and

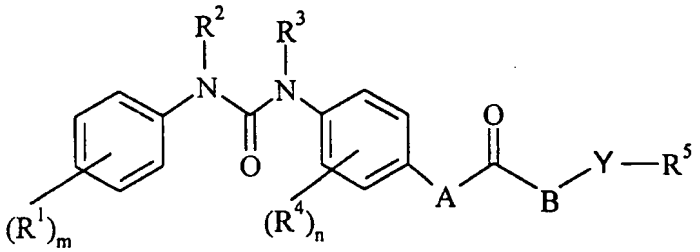
R^5 is an acidic functional group;

or a pharmaceutically acceptable salt or in-vivo hydrolysable derivative thereof.

2. A compound according to claim 1 wherein Y' is an alkylene chain which is interposed by a monocyclic ring system and/or a heteroatom.

3. A compound according to claim 1 wherein the group A' is orientated in the meta or para position with respect to the ureido group in formula (I), and most preferably A' is orientated para- to the ureido group in formula (I).

4. A compound according to claim 1 of formula (IA)



(IA)

wherein

A is nitrogen or NR^6, where R^6 is C_{1-6}alkyl, C_{2-6}alkanoyl or C_{1-6}alkoxycarbonyl;

B is oxygen or sulphur;

Y is a linker group connecting group B to group R^5 and containing up to 10 atoms where each atom is independently selected from carbon, oxygen, nitrogen and sulphur and may optionally comprise a monocyclic or bicyclic ring system or linker group Y and A can be taken together to form a 5 to 7 membered heterocyclic ring, optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

m is from 0 to 5;

n is from 0 to 4;

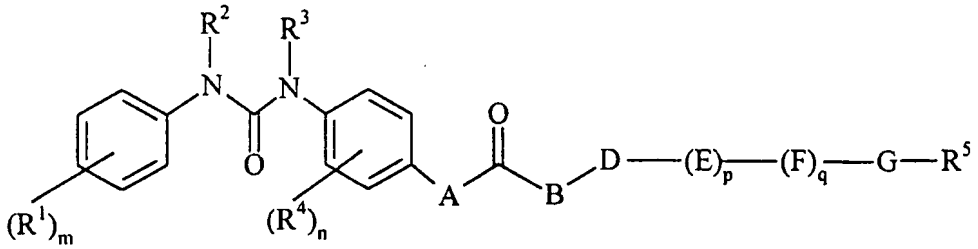
R^1 and R^4 are each independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6} alkylamino, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, N,N-di-[(C_{1-6}alkyl]carbamoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_tOH$ where t is 1 or 2, $-CO_2R^a$ and $CONR^aR^b$ where R^a and R^b are independently hydrogen or C_{1-6} alkyl or one of R^4 can be taken together with A to form a 5 to 7 membered heterocyclic ring optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{1-3} alkanoyl or C_{1-6} alkoxycarbonyl; and

R^5 is an acidic functional group;

or a pharmaceutically acceptable salt or in-vivo hydrolysable derivative thereof.

5. A compound according to any one of the preceding claims of formula (II)



(II)

wherein

A, B, R^1 to R^5, m and n are as defined in claim 4,

D and G are each independently C_{1-4} alkyl or C_{2-4} alkenyl and each carbon is optionally substituted with halogeno, hydroxy, amino, nitro, phenyl, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6} alkylamino, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, N,N-di-[(C_{1-6}alkyl]carbamoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_rOH$ where r is 1 or 2, $-CO_2R^7$ and $CONR^7R^8$ where R^7 and R^8 are independently

hydrogen or C_{1-6} alkyl, or D and A can be taken together to form a 5 to 7 membered ring, optionally substituted with up to 3 substituents independently selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

E is phenyl or a monocyclic heterocycle both optionally substituted with up to 3 substituents selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6}alkyl]amino, C_{2-6}alkanoylamino, C_{3-6} alkenoyl- amino, C_{3-6}alkynoylamino, C_{1-6}alkoxycarbonyl, N-C_{1-6}alkylcarbamoyl, N,N-di-[C_{1-6} alkyl]carbamoyl, C_{1-6}alkanoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_sOH$ where s is 1 or 2, $-CO_2R^9$ and $CONR^9R^{10}$ where R^9 and R^{10} are independently hydrogen or C_{1-6} alkyl or E and D can be taken together to form a bicyclic ring system, optionally substituted with up to 3 substituents selected from halogeno, hydroxy, amino, nitro, trifluoromethyl, trifluoromethoxy, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-[C_{1-6} alkyl]amino and C_{2-6}alkanoylamino;

F is selected from oxygen, sulphur, amino or $CR^{11}R^{12}$;

p and q are each independently 0 or 1;

R^{11} and R^{12} are each independently selected from hydrogen, halogeno, hydroxy, amino, nitro, phenyl, trifluoromethyl, trifluoromethoxy, cyano, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6} alkylamino, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, N,N-di-[(C_{1-6}alkyl]carbamoyl, C_{1-4}alkoxylC_{1-6}alkyl, $(CH_2)_uOH$ where u is 1 or 2, $-CO_2R^{15}$ and $CNNR^{15}R^{16}$ where R^{15} and R^{16} are independently hydrogen or C_{1-6} alkyl with the proviso that not more than one ring system can be formed from taking together two groups from R^4, A, D and E;

or a pharmaceutically acceptable salt or in-vivo hydrolysable derivative thereof.

6. A compound according to claim 5 wherein E is phenyl or a monocyclic heterocycle.

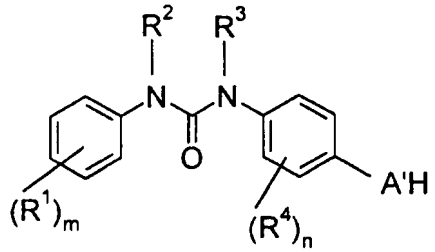
7. A pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof and a pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1 to 6 for use in a method of therapeutic treatment of the human or animal body.

9. The use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof in the production of a medicament for use in the treatment of a disease or medical condition mediated by the interaction between fibronectin and/or VCAM-1 (especially VCAM-1) and the integrin receptor $\alpha_4\beta_1$.

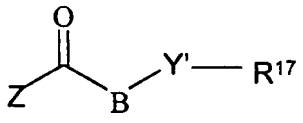
10. A process for preparing a compound of formula (I), a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof which method comprises either

(a) reacting a compound of formula (IV)



(IV)

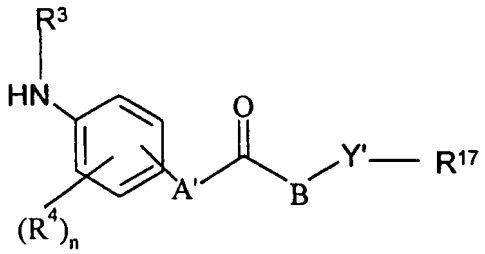
where A', R^1, R^2, R^3, R^4, m and n are as defined in relation to formula (I), with a compound of formula (V)



(V)

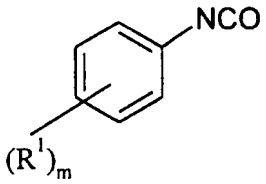
where B and Y' are as defined in relation to formula (I), Z is a leaving group, such as halo, and R^{17} is a group R^5 as defined in relation to formula (I) or a protected form thereof: or

(b) reacting a compound of formula (VI)



(VI)

where A', B, Y' R^3, R^4 and n are as defined in relation to formula (I) and R^{17} is as defined in relation to formula (V) with a compound of formula (VII)



(VII)

where R^1 and m are as defined in relation to formula (I);

and thereafter if desired or necessary,

i) removing any protecting groups; and.

ii) optionally forming a pharmaceutically acceptable salt or in vivo hydrolysable derivative.

INTERNATIONAL SEARCH REPORT

Inte ...al Application No
PCT/GB 00/01542

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C275/40 C07D295/15 C07D209/02 A61K31/17 A61K31/445
A61K31/496 A61K31/5375

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 04247 A (ZHENG ZHONGLI ;ADAMS STEVEN P (US); BIOGEN INC (US); ENSINGER CARO) 5 February 1998 (1998-02-05) cited in the application the whole document ---	1
A	WO 96 22966 A (BIOGEN INC ;ADAMS STEVEN P (US); LIN KO CHUNG (US); LEE WEN CHERNG) 1 August 1996 (1996-08-01) cited in the application the whole document -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2000	11/08/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ial Application No
PCT/GB 00/01542

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